Natural Tyrosinase Enzyme Inhibitors: A path from melanin to melanoma and its reported pharmacological activities

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Abstract

The skin containing melanin pigment acts as a protective barrier and counteracts the UVR and other environmental stressors to maintain or restore disrupted cutaneous homeostasis. The production of melanin pigment is dependent on tyrosine levels. L-tyrosine and L-dihydroxyphenylalanine (L-DOPA) can serve both as a substrates and intermediates of melanin synthetic pathway and as inducers and positive regulators of melanogenesis. The biosynthesis of melanin is stimulated upon exposure to UVR, which can also stimulate local production of hormonal factors, which can stimulate melanoma development by altering the chemical properties of eu- and pheomelanin. The process of melanogenesis can be altered by several pathways. One involves activation of POMC, with the production of POMC peptides including MSH and ACTH, which increase intracellular cAMP levels, which activates the MITF, and helps to stimulate tyrosinase (TYR) expression and activity. Defects in OCA1 to 4 affects melanogenic activity via posttranslational modifications resulting in proteasomal degradation and reducing pigmentation. Further, altering, the MITF factor, helps to regulate the expression of MRGE in melanoma, and helps to increase the TYR glycosylation in ER. CRH stimulates POMC peptides that regulate melanogenesis and also by itself can stimulate melanogenesis. The POMC, P53, ACTH, MSH, MC1R, MITF, and 6-BH4 are found to be important regulators for pigmentation. Melanogenesis can affect melanoma behaviour and inhibit immune responses. Therefore, we reviewed natural products that would alter melanin production. Our special focus was on targeting melanin synthesis and TYR enzyme activity to inhibit melanogenesis as an adjuvant therapy of melanotic melanoma. Furthermore, this review also outlines the current updated pharmacological studies targeting the TYR enzyme from natural sources and its consequential effects on melanin production.

Keywords: Melanoma, Tyrosinase inhibitors, Melanin, Melanogenesis, Skin Pigmentation, and Skin cancer.

Abbreviations

Cutaneous melanoma, CM

Acral lentiginous melanoma, ALM

Ultraviolet, UV

Tyrosinase, TYR

Hypoxia-inducible factor 1-alpha, HIF-1α

Proopiomelanocortin, POMC

Melanin stimulating hormone, MSH

Melanocortin 1 receptor - MC1R

Microphthalmia-associated transcription factor, MITF

Nitric Oxide synthase, NOS

Nicotinamide adenine dinucleotide phosphate, NADPH

Tetrahydro-biopterin, 6-BH4

Cyclin-dependent kinase inhibitor 2A, CDKN2A or p16

Cyclin-dependent kinase 4, CDK4Familial atypical multiple mole-melanoma, FAMMM

Nucleotide excision repair, NER

Neurofibromatosis type 1, NF1

Phosphatase and tensin homolog, PTEN

Tumor Protein 53, TP53

Telomerase Reverse Transcriptase, TERT

AT-rich interactive domain-containing protein 2, ARID2

Mitogen-Activated Protein Kinase, MAPK

L-3,4-dihydroxyphenylalanine, L-DOPA

5,6-dihydroxyindole, DHI

5,6-dihydroxyindole-2-carboxylic acid, DHICA

Tyrosinase-related protein 1, TYRP1

Tyrosinase-related protein 2, TYRP2

Epidermal growth factor, EGF

Endoplasmic reticulum, ER

Menkes copper transporter, MNK

Cysteine, Cys

Copper, Cu

Oculocutaneous albinism type 1, OCA1

Oculocutaneous albinism type 2, OCA2

Oculocutaneous albinism type 3, OCA3

Oculocutaneous albinism type 4, OCA4

Trans-Golgi Network, TGN

ER-associated protein degradation, ERAD

Adrenocorticotropic hormone, ACTH

Corticotropin releasing hormone, CRH

Hypothalamic pituitary adrenal, HPA

Vacuolar ATPase, v-ATPase

Melanogenesis-related gene expression,

MRGE

1.1. Introduction

Melanoma arises through malignant transformation of melanocytes, melanin producing cells, as shown in **Figure 1**. Due to its ability to metastasize to other parts of the body, it is one of the most aggressive types of all skin cancers (DeVita and Lawrence, 2008; Mitchell et al., 2020). It accounts for 1% of all skin tumors but has a mortality rate of up to 60% (Khazaei et al., 2019). Melanoma is of significant concern for the Caucasian population, and its incidence is increasing globally. In 2018, there were 2,87,723 cases and 60,712 deaths reported due to melanoma by WHO, which accounted for 0.6 % of deaths due to melanoma alone (WHO, 2019). The prevalence of cutaneous melanoma (CM) varies significantly among different populations, and these variations are due to distinct skin phenotypes and different levels of sun exposure. The acral lentiginous melanoma (ALM) is the most commonly seen variant with the Asian population (Phan et al., 2006). ALM is a malignant tumor or histological subtype of CM that occurs in the glabrous skin of the palms, soles, and nails, and it carries one of the worst prognoses among other subtypes. Furthermore, in contrast to other solid tumors, young to middle-aged individuals are more often affected by melanoma, and the incidence rate is augmented linearly between the age of 25 and 50 (Bressac-de-Paillerets et al., 2002; Leonardi et al., 2018). In addition, climate changes, increased amount of arsenic in water, ozone depletion, and numerous other factors like naevi have demonstrated to show direct associations with melanoma (Fabbrocini et al., 2010).

Melanin protects from ultraviolet radiation (UVR) induced malignant transformation of melanocytes. However, its role in melanoma progression is complex. This is recently discussed by Slominski and co-workers (Slominski et al., 2022), stated that melanin protects against the development of skin cancers including cutaneous melanoma, and its presence is necessary for the transformation of melanocytes (Slominski et al., 2022). Melanocytes produce

melanin, which contains both eumelanin, and pheomelanin, through a series of oxidoreduction processes. The enzyme tyrosinase (TYR) catalyses the hydroxylation of L-tyrosine to L-DOPA, which is further oxidized to DOPAquinone, a starting process of melanogenesis (Hearing and Tsukamoto, 1991; Pawelek et al., 1992; Pawelek, 1993; Chung et al., 2018). The melanin is then deposited in the melanosomes, which are transported to keratinocytes, finally defines the skin and hair colour (Wasmeier et al., 2008; Garibyan and Fisher, 2010; Kim et al., 2018). The coordinated levels of eumelanin and pheomelanin regulate the skin physiological adaptation upon exposure to UVR. This shows a complex role of melanogenesis, defined by the chemical properties of melanin and the nature generating pathways such as eu- and pheomelanogenesis, which may affect the process of melanoma development. Thus, eumelanin acts as an effective antioxidant, and acts as a sunscreen and is believed to provide radio and photoprotection, whereas pheomelanin, generates mutagenic environment after exposure to UVR. Intermediates of melanogenesis are highly reactive and have cytotoxic, genotoxic, and mutagenic activities. Melanogenesis can stimulate glycolysis and hypoxia-inducible factor 1-alpha (HIF-1α) (Slominski et al., 2014), which can lead to the progression of melanoma and can affect resistance to immunotherapy (Slominski et al., 2022). Thus, dysregulated levels of eu- and pheomelanin can lead to various skin pathological conditions such as skin diseases and pigmentary disorders (Garibyan and Fisher, 2010). Although the primary role of melanin is to defend the skin against UVR and injury (Brenner and Hearing, 2008; Schallreuter et al., 2008), it can affect radiotherapy (Brozyna et al., 2016) and overall disease-free survival in patients with stage III and IV melanoma (Brozyna et al., 2013). As TYR plays a pivotal role in melanogenesis, it is considered to be a putative therapeutic target for combating melanoma (D'Mello et al., 2016).

Given the increasing incidence of melanoma, considerable attention has focused on to develop newer and improved strategies such as use of pro-drugs for treating the disease. The

pro-drugs are activated by TYR targeting melanoma, and could be an interesting *in-situ* tool for the treatment of melanoma, but it tends to form toxic metabolites and thus require alternative approach therapy (Rooseboom et al., 2004; Gasowska-Bajger and Wojtasek, 2008; Jawaid et al., 2009). Natural products including phytochemicals are reported to possess a wide number biological activities mainly flavonoids, alkaloids, glycosides, terpenoids (Hasanpourghadi et al., 2017), and recently have gained more attention towards chemotherapy, and also shows promising activity against various tumors (Nobili et al., 2009; Turek et al., 2016; Shanmugam et al., 2016). Further, based on these collated reports natural products could be a potential weapon in combating cancer (Naviglio and Della Ragione, 2013; Shanmugam et al., 2016). Therefore, this review discusses in detail on the TYR regulation, and its role in melanogenesis, with potential targeting TYR in treatment of melanoma.

1.2. Role of UVR in melanoma

The UVR from the sun is considered to be the primary ecological reason in the development of melanoma (Gilchrest et al., 1999; Leonardi et al., 2018). Melanoma develops when melanocytes proliferate rapidly, occurs due to UVR -induced DNA mutations, which account for about 65% of melanoma occurrences in skin (Armstrong, and Kricker, 1993). The skin, is a self-regulating protective barrier, empowered with sensory capabilities to counteract the environmental stress and helps to maintain and restore the disrupted cutaneous homeostasis (Slominski and Wortsman, 2000; Slominski et al., 2012; Slominski et al., 2022). These functions are completely coordinated by cutaneous neuro-endocrine system that communicates with the central nervous, endocrine, and immune systems in a bidirectional way, and plays a potential role in controlling body homeostasis (Slominski and Wortsman, 2000; Slominski et al., 2022). However, the energy obtained from UVR is absorbed by skin, which triggers the mechanisms that defend skin integrity, and also regulates the body homeostasis (Slominski et al., 2018). Therefore, the UVR acts by touching the brain and central neuroendocrine system

in order to reset the body homeostasis (Skobowiat et al., 2011, Slominski et al., 2018). The epidermal melanin has an important physiological implication in humans, were higher content of melanin helps to protect against UVR-induced skin damage via optical and chemical properties (Ahene et al., 1995). The pigment amounts were found higher in regions of lower latitude and higher UVR levels were observed in skin. This may be directly associated with humans in early hominids having dark and dense coloured hair. Post et al., reported on the closely related primate i.e., chimpanzees, and showed to exhibit white or light colour pigment in the epidermal layer (Post et al., 1975). Interestingly, chimpanzees have active melanocytes that are present in the epidermis of those areas, which are directly exposed to UVR (Montagna and Machida, 1966).

Therefore, in order to maintain thermal balance in human epidermis, which leads to an progressive increase in demands for heat dissipation, and further resulting from enhanced blood flow to the brain (Pagel and Bodmer, 2003). Thus, an increased epidermal melanization occurs due to high exposure to UVR in humans, which potentially could lead to adverse effects, such as sunburns and causes damage to the sweat glands resulting in the suppression of sweating and abnormal thermoregulation (Pandolf et al., 1992), and can induce carcinogenesis, and inactivation of nutrient by photolysis (Branda and Eaton, 1978; Slominski et al., 2004).

The epidermal melanocytes, are pigment producing and secretary cells of the neural crest that communicates with multiple targets. Slominski et al., reported on the normal epidermal melanocytes, which are sensory and regulatory cells operating in the context of regulatory network that helps to maintain the epidermal homeostasis in humans (Slominski et al., 1993a; Slominski, 2009a). Thus, the functions of altered melanocyte, plays a major role in other diseases like skin disease, and racial pigmentation, which may affect the cutaneous functions (Slominski et al., 1993; Barsh, 1996).

The activation of the proopiomelanocortin (POMC) expression, production and release of POMC derived peptides including ACTH, melanocyte stimulating hormone (MSH) and β-endorphin from keratinocytes, helps to stimulate the melanocytes or fibroblasts causing melanocyte differentiation (Slominski et al., 2000; Slominski et al., 2004). These melanocytes respond to the MSH via polymorphic receptor melanocortin 1 receptor (MC1R). Thus, activation of this receptor causes increase in the cAMP levels and further activates the transcription of microphthalmia-associated transcription factor (MITF) (Garibyan and Fisher, 2010). This signalling mechanism results in the initiation of melanin synthesis through stimulation of TYR, and leads to the protection of keratinocytes from DNA damage. In the keratinocytes, UVR activates nitric oxide synthase (NOS) type 1, leading to increased nitric oxide and TYR levels, causing subsequent acceleration of melanogenesis. The activity of the NOS cofactors, including calcium, nicotinamide adenine dinucleotide phosphate (NADPH), and tetrahydro-biopterin (6-BH4), were also elevated upon exposure to UVR. Among these cofactors, activation of 6-BH4 leads to the activation of NOS type 1, but still the mechanism involved in it is unclear (Roméro-Graillet et al., 1997). Apart from that, 6-BH4 is also involved in modulating the TYR enzyme activity. The 6-BH4 is a vital cofactor and an electron donor in the conversion of L-phenylalanine to L-tyrosine occurs via hydroxylation. It acts as a rate-limiting factor in controlling the production of L-tyrosine (Schallreuter et al., 1994). Additionally, the redox switch between 6-BH4 and 6-biopterin controls TYR activity and regulates melanogenesis, but photo-oxidation of 6-BH4 occurs upon exposure to UVR and could lead to elevated TYR activity (Wood et al., 1995). Thus, exposure to UVR alters the regulation of NOS type 1 activity, tyrosine production, and TYR activity. Therefore, this showed to elevate the expression of UVR-induced 6-BH4 levels and increased photo-oxidation, which may also lead to cancer conditions (Wood et al., 1995). In addition, melanoma develops as a result of interactions between genetic and environmental factors. Excessive exposure to

UVR, can cause increase in the melanoma penetrance in melanoma-prone families. For instance, in a study on melanoma-prone families, patients' with "9p-linked" gene, were altered due to excessive exposure to UVR regardless of their skin type showed increased chance of developing melanoma (Cannon-Albright et al., 1994).

Of note, about 5-12% of melanoma with the distinct mutation has been reported to be of hereditary origin (Rebecca et al., 2012). These mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A* or p16) and cyclin-dependent kinase 4 (CDK4) are most frequently identified in the families prone to familial atypical multiple mole-melanoma (FAMMM) (Gruis et al., 1995; Zuo et al., 1996; Soura et al., 2016). Further, changes in the *CDKN2A* gene mutation showed to possess about 40% of familial melanomas, which resulted in defective tumor suppressor proteins p14 (*p14ARF*) and p16 (*p16INK4A*), and further stabilizes p53 gene by regulating the G1 checkpoint (Rebecca et al., 2012; Shain and Bastian, 2016). Interaction of p16 with CDK4 results in cell cycle arrest, whereas mutations in p16 (p16INK4A), helps to inhibit the binding of p16 to CDK4, and thereby interrupts the cell cycle arrest (Mehnert and Kluger, 2012). Mutation in the nucleotide excision repair (NER) pathway, which is another group of germline mutation, identified to augment the risk of developing melanoma (Davis et al., 2019). These mutations are more pathogenic, and are less common. Further, intensive exposure to UVR can causes DNA lesions, which are removed by NER mechanism. Therefore, genetic mutations in NER pathways results in increased UVR-induced unrepaired DNA damage.

Melanomas are also associated with recurrent somatic mutations. Most frequently, the key mutations occur in the signalling pathways are (a) *BRAF*, *NRAS*, and neurofibromatosis type 1 (NF1), which plays an important role in regulating the proliferation of cells (Scolyer et al., 2011), (b) Phosphatase and tensin homolog (PTEN) and *KIT* that coordinates the growth and metabolism (Read et al., 2016), (c) Tumor Protein 53 (TP53) which regulates resistance to

apoptosis (Scolyer et al., 2011), (d) Telomerase reverse transcriptase (TERT) – regulates replicative lifespan (Horn et al., 2013; Read et al., 2016), (e) AT-rich interactive domain-containing protein 2 (ARID2) – responsible for cell identity (Scolyer et al., 2011) and (f) *CDKN2A* – responsible for cell cycle arrest (Scolyer et al., 2011; Read et al., 2016). Although melanomas arise from somatic mutations, most of them could develop due to acquired mutations. For instance, mitogen-activated protein kinase (MAPK) is the most commonly mutated pathway, and these mutational events were prevalent in 70% of melanoma patients (Scolyer et al., 2011). Similarly, about 80% of them contain *BRAF* mutations, were V600E is the most common mutation of BRAF that is over >85%, and activates the downstream MAPK oncogenic pathway. Together, it is apparent that MAPK cascades have potential implications in UVR-induced carcinogenesis. Yet, the mechanism by which MAPK cascades orchestrate UVR exposure-driven melanoma remains elusive (Bode and Dong, 2003).

1.3. Role of melanin and melanogenesis in regulating cellular metabolism

The movement of mature melanosomes from melanocytes into keratinocytes via lysosomal compartment, occurs in the upper epidermal layer forming melanin granules. Furthermore, precise mechanism of melanin breakdown or degradation remains to be investigated. The melanin is highly resistant to enzymatic lysis, and reports showed that phagosomal NADPH oxidase enzyme degrades the melanin via oxidation (Borovansky and Elleder, 2003). Unlike those in overlying epidermis, the melanin granules remain intact in the hair shaft and this occurs mainly in the black hair shaft containing eumelanogenic melanosomes, which are often seen in East-Asian individuals containing high-density pigment granules.

Melanin can reduce the effect of UV penetration to blood in humans. The highest UV absorption for oxyhemoglobin can be identified at a wavelength of 545 nm, which causes strong erythema reaction with subsequent pigmentary response with individuals having light

skin. Therefore, when exposed to UVR, melanin undergoes photosensitization producing superoxide radicals, causing harmful injury to cells. This process could possibly lead to a condition called cell neoplasia, causing low proliferation rate in normal skin cells (Furuya et al., 2002), and consisting of a linkage between melanin production and UVR-induced DNA damage, i.e., responsible for maintaining the skin homeostasis and tanning (Gilchrest and Eller, 1999). Therefore, understanding pathophysiology of pigmentation, occurs mainly due to the exposure of melanin to various toxic metabolites, resulting in higher melanin granules and deposition, which could be possible reason of pigmentation (Lindquist, 1973; Slominski et al., 2004).

Melanin plays an imperative role in preventing melanoma formation (Gilchrest et al., 1999), as it protects the skin from UVR-induced DNA damage and genetic changes. However, repetitive exposure decreases its protective function, resulting in cancer progression (Armstrong and Kricker, 1993). TYR plays a crucial role in the synthesis of melanin as it is the rate-limiting enzyme of the pathway, possessing both monophenolase and diphenolase activities, which enable oxidation of tyrosine to L-DOPA, and is said to be the first and most critical step in the synthesis of melanin. Melanin synthesis involves hydroxylation of L-tyrosine to L-DOPA and subsequently its oxidation to DOPA-quinone. Next, DOPA-quinone cyclizes to form DOPA-chrome, leading to the production of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA). TYR catalyses the oxidative polymerization of DHI. TYR- related protein 1 catalyses the oxidation of DHICA and leads to the formation of melanochrome and converted to an insoluble eumelanin pigment (Raper, 1928; Korner and Pawelek, 1982; Wang and Hebert, 2006). Also, in the presence of cysteine and glutathione, DOPA-quinone is converted to 5-S-cysteinyl-DOPA and cystathionyl-DOPA, respectively then later converted to pheomelanin (Pillaiyar et al., 2015).

1.4. Tyrosinase enzyme and its intrinsic roles

The key regulatory enzyme of melanogenesis, is TYR a product of c-locus that maps to the chromosome 11q14–21 in humans (Barton et al., 1988) and chromosome 7 in mice, respectively, consisting of five exons and four introns (Kwon, 1993; Thody, 1995; Nordlund et al., 1998). The TYR mRNA generates several alternatively spliced products while posttranscriptional processing occurs (Shibahara et al., 1988; Porter and Mintz, 1991; Kelsall et al., 1997; Le Fur et al., 1997), of which some are translated to protein products expressing TYR activity (Muller et al., 1988; Ruppert et al., 1988). It is proposed that the obtained products from TYR mRNA could be best served as regulatory protein (Slominski and Paus; 1990; Slominski and Paus; 1994), and acts as a receptor for L-tyrosine and L-DOPA (Slominski and Paus, 1994). Also, it is noted that non-functional TYR proteins express non-melanocytic cells (Haninec and Vachtenheim, 1988; Tief et al., 1998). There is evidence that L-tyrosine and L-DOPA, besides serving as a substrates and intermediates for melanogenesis, and also act as a bioregulatory agents, and inducers, which shows positive regulators of melanogenesis, leading to regulation of the cellular functions (Slominski and Paus, 1990; Slominski et al., 2012).

TYR catalyses three distinct reactions in the melanogenic pathway; i.e., hydroxylation of L-tyrosine, dehydrogenation of L-DOPA, and dehydrogenation of DHI; where L-DOPA serves as cofactor in the first and third reactions (Lerner and Fitzpatrick, 1950; Korner and Pawelek, 1982; Pawelek and Korner, 1982; Hearing and Tsukamoto, 1991). Both hydroxylation of tyrosine and dehydrogenation of L-DOPA requires single step, where the substrate binding site are the same, and the reaction involves exchange of electrons with copper atoms generating orthoquinone and water as final products (Nordlund et al., 1998; Riley, 2000; Land et al., 2003a; Land et al., 2003b; Slominski et al., 2004). Slominski et al., reported on the role of L-tyrosine, L-DOPA, and TYR as a positive-regulators of melanogenesis in Bomirski Ab amelanotic hamster melanoma cells. Their findings showed that synthesis of subcellular

level of melanogenesis is initiated by L-tyrosine and is further regulated by TYR and L-DOPA, which serves as a second messenger to tyrosine hydroxylase activity (Slominski et al., 1989; Slominski and Paus, 1994).

The TYR protein structure is different among highly conserved species and shows high homology with other tyrosinase-related proteins, such as tyrosinase-related protein 1 (TYRP1) and 2 (TYRP2). In this protein the TYR comprises of NH_2 terminal domain signalling peptide responsible for intracellular trafficking and processing, the epidermal growth factor (EGF)-like/cysteine-rich domain, has two histidine regions, and copper (Cu) binding site with a cysteine region acting as an important catalytic domain, and COOH-terminal with hydrophobic transmembrane segment and a cytoplasmic tail (Kwon et al., 1987; Shibahara et al., 1988; Kwon, 1993; Nordlund et al., 1998). These transmembrane and cytoplasmic domains are important for targeting the enzyme to melanosome (Jimbow et al., 2000a; Jimbow et al., 2000b; Selaturi, 2000), while the NH_2 terminal with cysteine region may serve as a protein binding/regulatory domain unrelated to enzymatic function. Later, the newly synthesized TYR has about 55–58 kDa molecular mass with an isoelectric point of 4.2. These requires proper folding of TYR protein and is crucial for further transport to Golgi apparatus in the endoplasmic reticulum (ER). Therefore, the proteolytic cleavage of the transmembrane portion of newly synthesized enzyme generates two soluble forms: a 53-kDa unmodified protein, or a 65-kDa glycosylated TYR, which may be active in the melanosome or secreted into the extracellular environment. After glycosylation in the trans-Golgi complex, there is an increase in the size of TYR of about 65–75 kDa or even 80 kDa (Hearing and Tsukamoto, 1991; Sanchez-Ferrer et al., 1995; Del Marmol and Beermann, 1996a; Del Marmol et al., 1996; Jimbow et al., 2000). The higher molecular mass of TYR (Slominski A and Costantino, 1991; Slominski et al., 1991a; Slominski et al., 1991b; Sanchez-Ferrer et al., 1995; Del Marmol and Beermann, 1996a), may possess tight complexes with other melanogenic (Orlow et al., 1994), or high-

molecular-weight TYR proteins. When copper ions, are necessary for the enzymatic activity, they integrate into apo-TYR, which is still unclear. However, recent data suggests that the Menkes copper transporter (MNK) is required for copper loading of TYR enzyme necessary for its activation (Petris et al., 2000). The catalytic site of TYR is represented by two copper atoms ligated to six histidine residues.

TYR is a metalloenzyme with a highly conserved bi-copper active center (Ramsden and Riley, 2014); however, its structural properties are distinct in bacteria, plants, and mammals (Solano, 2014). In the mushrooms and vertebrates, the TYR catalyses the initial steps in forming the melanin pigment using tyrosine. In contrast, the plants use the composition of phenols as a substrate (Casanola-Martin et al., 2014). In mammals, it is expressed abundantly in melanocytes, but it is also present in the epithelial layer of the retina, iris, and ciliary parts of the eye (Saeki and Oikawa, 1980). TYR is classified under type-I membrane glycoproteins and consists of three conserved domains; N-terminal signal domain, solitary transmembrane α-helix, and C-terminal cytoplasmic domain. The N-terminal domain of TYR is responsible for the catalytic activity. It comprises of 17 cysteines (Cys) residues present as 3 clusters and 7 N-linked glycosylation sites present throughout the region. Among 17 Cys residues, 15 residues are freely available for the disulphide bonding, whereas one residue is removed by signal sequence locally and another residue is removed in the cytoplasmic tail. The solitary hydrophobic transmembrane domain consists of 26 amino acid sequences and it anchors the TYR into the melanosome membrane (Wang and Hebert, 2006). This cytoplasmic domain harbors a melanosome sorting signal that traffic the protein to the melanosomal membrane. The two Cu atoms in the active cite of the enzyme are harmonized with three histidine residues that anchor dioxygen binding to the peroxy configuration (Ramsden and Riley, 2014). This dioxygen bonds with Cu at the active site comprises of the amino acid sequence of His162,

184, and 193, which are referred to as CuA whereas, CuB includes His345, 349, and 371, respectively (Wang and Hebert, 2006).

The enzyme TYR possesses four oxidation states, met-, oxy-, deoxy-, and deact-TYR, which play an imperative role in melanin production (Ramsden and Riley, 2014). Oxy-TYR or oxygenated form entails two tetragonal Cu (II) atoms. Both of them are coordinated with strong dual equatorial and single weak axial N_{His} ligand, and two Cu atom centers that are linked by the peroxide, forming exogenous oxygen molecule. Likewise, met-TYR comprises of two tetragonal Cu (II) ions bridged by water or hydrophobic ligands. In this form, other than peroxide, there are few hydroxide ligands that are also attached exogenously to the Cu binding site. Deoxy-TYR comprises of twin Cu (I) ions, which synchronizes parallel to the met form, and lacks the hydroxide bridge in the ring structure. Therefore, the enzyme that is achieved after purification will comprise of both met and oxy forms in the ratio 85:15 (Chang, 2009). The met-TYR has a null role in catalysing the conversion of substrates i.e., catechol and phenols to ortho-quinones. Conversely, the deoxy-TYR oxidizes phenols and catechols in the monophenolase and diphenolase phases, respectively. The catechol oxidation in monophenolase phase by oxy-TYR leads to elimination of Cu atoms in the active site and irreversible formation of deoxy-TYR, which subsequently results in deactivation of the enzyme (Ramsden and Riley, 2014).

Defects in the TYR gene leads to a condition called as oculocutaneous albinism type 1 (OCA1) (Tomita et al., 1989; Takeda et al., 1990; Oetting and King, 1999). Due to the mutations in the Cu binding sites, the entire coding sequence of the gene is susceptible to mutations, which further leads to abnormalities in splicing (Oetting and King, 1999). Thus, the mutant TYR proteins are degraded by proteasomes enzyme, and allowing it to pass to the Golgi apparatus for glycosylation and further stops the transport to premelanosomes (Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Kushimoto et al., 2003; Toyofuku et al., 2001a;

Toyofuku et al., 2001b). Similarly, in oculocutaneous albinism type 3 (OCA3), the TYRP1 mutated is retained within ER and the process of normal TYR is terminated leading to proteasomal degradation and reduces pigmentation (Kushimoto et al., 2003; Toyofuku et al., 2001a; Toyofuku et al., 2001b). In case of oculocutaneous albinism type 2 (OCA2) and type 4 (OCA4), the TYR from trans-Golgi network (TGN) to melanosomes is disrupted (Chen et al., 2002; Toyofuku et al., 2002; Costin et al., 2003; Kushimoto et al., 2003). The experimental evidence suggested in various melanocytes, showed that ER is an essential step for TYR maturation, targeting melanosomes, and is an important step in the production of melanin pigment (Halaban, 2000; Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Halaban et al., 1997; Halaban et al., 2000). Thus, the defects underlying OCA1 via OCA4 showed melanogenic activity *in-vivo*, depends on the posttranslational pathways, of which the most important is the processing of TYR. In fact, the levels of TYR mRNA were found to be similar in both European and African individuals in cultured melanocytes (Iozumi et al., 1993), and also shows that TYR gene expression finds to be same among different human groups (Iwata et al., 1990; Fuller et al., 2001). On the other hand, dysregulation of the TYR melanogenic activity can be due to the lack of melanosomes, resulting in the accumulation of enzyme or blockade in the translocation from TGN to melanosomes (Bomirski et al., 1988; Slominski, 1988; Slominski et al., 1989), in the presence of intracellular TYR inhibitors or protein kinase-dependent phosphorylation (Wong and Pawelek, 1975; Korner and Pawelek, 1977; Kameyama et al., 1989; Park and Gilchrest, 1999; Slominski et al., 2004).

A plethora of studies suggests that UVR modulates the expression of TYR. The transcription factor MITF acts as a primary regulator of melanogenesis-related gene expression (MRGE) (Fuller et al., 1990), which subsequently regulates the mRNA levels of TYR and/or MITF in cultured melanoma (Lin et al., 2002; Ando et al., 2007). Therefore, increase in the glycosylation of TYR enzyme in the ER helps to inhibit the folding and maturation of melanin,

423 resulting in pigmentation (Imokawa, 1989). Thus, proteostasis of TYR is governed by the ER-
424 associated protein degradation (ERAD) regulated by the ubiquitin-proteasome system, E3
425 ligases Doa10p and Hrd1p have been shown to ubiquitinate TYR, resulting in subsequent
426 degradation (Hammond and Helenius, 1995; Bordallo et al., 1998). Further, transportation of
427 TYR into melanosomes for melanogenesis is also dependent on ER. However, mutations in
428 TYR result in TYR sequestration in ER and binds to ER-chaperones, calnexin, and calreticulin
429 (Toyofuku et al., 2001a; Toyofuku et al., 2001b). This accumulated TYR is degraded through
430 ERAD and thus inhibits its function (Smith et al., 2004). Therefore, ER plays a significant role
431 in the regulation of TYR.

432 The pH critically modulates the TYR activity, and acidic pH is appropriate for its
433 optimal tyrosine hydroxylase activity (Bhatnagar et al., 1993). The early melanosomes contain
434 an acidic environment (Moellman et al., 1988; Raposo et al., 2001), where pH increases as the
435 melanosomes mature, creating an optimal environment for TYR activity (Tucker and
436 Goldstein, 2003). The incidence of melanoma is intensively increasing in Western countries
437 (Fuller et al., 2001). In the Caucasian population, TYR activity for the synthesis of melanin is
438 relatively less when compared with the darker skin-coloured population, even though the level
439 of TYR mRNA and the enzyme are in abundance (Giebel et al., 1991), and the gene sequence
440 were reported similar in both black as well as Caucasian population (Tachibana et al., 1996;
441 Spritz et al., 1991). Also, the pH of melanosome and activity of TYR is controlled by the
442 expression of vacuolar ATPase (v-ATPase) (Giebel et al., 1991; Ito and Wakamatsu, 2003). In
443 the Caucasian population, higher expression of v-ATPase resulted in increased H^+ levels and
444 produces an acidic environment in melanosomes. Conversely, in the African population, the
445 expression of v-ATPase is low and hence requires to maintain acidic pH. Further, the melanin
446 content in black skin is six times higher when compared to the white skin, particularly the
447 levels of eumelanin (Kollias et al., 1991), whereas it was not so true in the case of pheomelanin

(Brenner and Hearing, 2008). In the black skin population, the melanosomes exist in single forms and works efficiently in the keratinocytes. In contrast, white skin forms clusters and translate as complex and work less efficiently (Pillaiyar et al., 2018). Together, these distinct mechanisms result in lower melanin production, which increases the risk and incidence of melanoma in Caucasians population. Therefore, it is apparent that the function of TYR is influenced by its substrates, cofactors, and cellular environmental factors. Also, the oxidation mechanism by the two Cu atoms present in the active site has been shown to influence the functions of TYR.

1.5. Role of POMC Expression in Skin

MSH was the first POMC peptide detected in the skin (Thody et al., 1983). Skin expresses the POMC gene and produces adrenocorticotropic hormone (ACTH) and □-endorphin (Slominski et al., 1993; Slominski and Mihm, 1996; Wintzen and Gilchrest, 1996; Luger et al., 1998; Slominski and Pawelek, 1998). The POMC gene transcription and translation in the mammalian skin was originally observed in C57BL/6 mice (Slominski et al., 1991; Slominski et al., 1992). Subsequently, POMC gene expression has been found in human skin, as well as in cutaneous cell culture systems (Slominski, 1991; Slominski, et al., 1991; Slominski, et al., 1992; Farooqui et al., 1993; Schauer et al., 1994; Chakraborty et al., 1995; Kippenberger et al., 1995; Slominski, et al., 1995; Slominski, et al., 1996; Chakraborty et al., 1996; Ermak and Slominski, 1997; Nagahama et al., 1998; Slominski, 1998; Slominski, et al., 1999; Slominski et al., 2000).

1.6. Role of corticotropin releasing hormone (CRH) in the epidermis

CRH has an important role in regulating the protective and homeostatic functions of the skin (Slominski et al., 2001; Slominski et al., 2013), where the synthesis of DNA occurs in the epidermal and dermal compartments, showing proliferation of cells in the keratinocytes (Slominski et al., 1999). Thus, stimulation of DNA synthesis is mainly achieved by adding

CRH to the telogen and anagen IV, in the keratinocytes (Slominski et al., 1999). However, in anagen II, the CRH has a opposite effect towards DNA synthesis, which showed to enhance the dermal DNA synthesis (Slominski et al., 1999). These reports suggest that CRH plays an important role in the proliferation of epidermal keratinocyte. Further, the exogenous CRH showed activity on the cellular levels targeting epidermal cycle dependent expression of CRH-related receptors. In order to determine the various contributing factors involving the exogenous CRH, which also includes endogenous production of CRH and CRH activated production of ACTH and MSH. It is well established that CRH at the systemic level regulates corticosterone (Nicolaides et al., 2015). Further, reports suggested that increased levels of CRH substantially increases the levels of corticosterone by stimulating the hypothalamic pituitary adrenal (HPA) axis (Wilson et al., 1998). Further, increased levels of glucocorticosteroid clearly showed to possess an anagen-inhibitory effect on CRH implants (Paus et al., 1994; Paus, 1996; Paus et al., 1999; Slominski et al., 2000).

1.7. Skin as a Target for POMC Peptides

The studies on the POMC knock-out mice model showed that surprisingly, these animals survived till the adulthood (Yawsen et al., 1999). This genotype led to the adrenal insufficiency, and leads to defects in melanin pigmentation (Yawsen et al., 1999). This is similar to patients with pituitary POMC gene mutations, which generates allelic forms with defective production of POMC protein (Hinney et al., 1998; Krude et al., 1998). Thus, the affected individuals possess red hair pigmentation, and shows adrenal insufficiency. There is a clinical report on excess POMC peptide syndromes that confirms skin as a potential target for POMC-derived peptides (Lerner and Mcguire, 1961; Moellmann et al., 1988; Lerner, 1993; Pawelek, et al., 1992; Pawelek, 1993; Slominski et al., 1993; Siegrist and Eberle, 1995; Wintzen and Gilchrest, 1996; Jordan and Jackson, 1998; Luger et al., 1998; Luger et al., 1999). For example, humans with pathologically increased levels of plasma ACTH levels in case of

Addison disease or excessive ACTH production by tumors in case of Nelson syndrome, showed hyperpigmentation and skin atrophy (Eberle, 1988), whereas administration of MSH or ACTH peptides showed in the stimulation of melanogenesis (Lerner, 1993; Lerner et al., 1961). Also, continuous administration of ACTH in humans causes acne, skin atrophy, hyperpigmentation, and hypertrichosis (Eberle, 1988). Thus, elevated levels of α-MSH in the serum concentrations are directly associated with skin pigmentation (Pears et al., 1992). Additional research performed on human and animal models, showed that immune, epidermal, adnexal, vascular, and dermal structures possessed additional targets for POMC peptides (Slominski et al., 2000). However, the effect of POMC on melanin pigmentation is conditional on functional agouti protein, since knocking of POMC gene in C57BL/6 mice, does not affect melanin production (Slominski et al., 2005).

1.8. Effects of CRH in malignant melanocytes

The CRH has a direct effect on melanocytes, where a study on hamster melanoma cell line, showed further insight into the mechanism of CRH action in the skin (Fazal et al., 1998; Slominski et al., 1999, 2000). Skin cells express corticotropin releasing hormone receptor 1 (CRH-R1) gene, where in case of melanoma, the CRH-R1 mRNA transcription was 2.5 kb long, being 0.2 kb shorter than that detected in normal skin cells (Slominski et al., 1999). Melanocytes and melanoma cells express G protein-coupled CRH-R1, which responds to CRH and acts mainly by activation of cAMP, IP3, and other mediated pathways and also acts by activating the Ca^{+} signalling to modify the melanocyte phenotype (Slominski et al., 2001; Slominski et al., 2006a; Slominski et al., 2006b). In normal and immortalized melanocytes, CRH inhibits the cell proliferation in serum-containing medium, inhibits early and late apoptosis in serum free media (Slominski et al., 2006a). Concerning melanoma cells, the effect was found to be heterogenous depending on the cells (Slominski et al., 2006a; Carlson et al., 2001). The variability in CRH action in the melanoma cells could be explained by co-

expression of alternatively spliced CRH-R1 isoforms on the same cells that helps to modify the action of the CRH-R1α isoform (Slominski et al., 2001; Slominski et al., 2006b). Of significance, antimelanoma effect for selective CRH-R1 agonists has already been observed in *in-vivo* experimental models of melanoma (Carlson et al., 2001). Accordingly, selective targeting of CRH-R1 has been proposed for the treatment of malignant tumors that also include melanoma (Patent No: WO0153777).

1.9. Pharmacological approaches modulating TYR activity

A wide number of compounds from medicinal plants have been reported to inhibit melanogenesis by modulating the glycosylation of TYR enzyme (Imokawa and Mishima, 1982; Imokawa, 1989; Mineko et al., 1992; Petrescu et al., 1997; Pillaiyar et al., 2017). Selective approaches targeting TYR expression, degradation, and maturation are emerging as promising leads, including inhibition of TYR enzyme mRNA transcription (**Table 1**), abnormal maturation, acceleration of enzyme degradation, and direct modulation of catalytic activity. The TYR activity modulators were reported to treat hyper- and hypo-pigmentary skin disorders (Pillaiyar et al., 2017). These TYR enzyme inhibitors are commonly used in commercial cosmetics, mainly as a skin whitening agent (Pillaiyar et al., 2017). These medicinal plants and their phytochemicals showing inhibitory and stimulatory effect on TYR are shown in **Tables 2 and Table 3**.

Conversely, many inhibitors targeting TYR have been reported to exhibit lesser adverse effects (Burnett et al., 2010). Intriguingly, it has been revealed that some of the glycosylation inhibitors, glucosamine, and tunicamycin, do not affect TYR expression, but inhibit the synthesis of melanin (Swanson et al., 2001). Together, diverse research approaches are warranted since the conventional methods of TYR enzyme modulators have challenged its effects in melanoma therapy. Consequently, the current discoveries in melanoma therapy are

advancing by embracing technology, including nanotechnology-assisted targeted delivery (Swanson et al., 2001).

1.9.1. POMC gene expression and peptides production in C57BL/6 Mice

POMC is regulated by CRH signal that affects the function of melanocytes and melanoma cells (Slominski et al., 2013). Furthermore, the role of POMC-derived peptides in the regulation of melanogenesis is well illustrated in POMC knock out C57BL/6 mice model. The results showed that the POMC transcription of C57BL/6 mice skin is 0.9 kb long, and the POMC protein, detected with an anti-□-endorphin antibody, which has a molecular mass of 30–33 kDa (Slominski et al., 1992). This form of POMC mRNA has been observed in the epidermis and epidermal Thy-11 dendritic cells in C57BL/6 mice skin (Farooqui et al., 1993; Farooqui et al., 1995; Slominski et al., 2000). Slominski, demonstrated the effect on non-agouti C57BL/6 mice, which are POMC deficient, where the skin types are negative for mRNA, whereas the melanin pigmentation are similar to that of the control C57BL/6 $POMC^{+/+}$ and wild-type C57BL/6 mice. Therefore, C57BL/6 $POMC^{-/-}$ mice produces eumelanin hair pigmentation, in absence of local and systemic αMSH or ACTH ligands (Slominski et al., 2005). Various others studies showed that αMSH and ACTH could regulate melanin pigmentation in rodents and humans (Nordlund et al., 1988; Lerner, 1993; Slominski et al., 2000). These effects of melanocortin peptide are mediated by signal cascades that includes their binding to G protein-coupled MC1-R, activation of cAMP-dependent pathways, and stimulation or induction of eumelanogenesis (Nordlund et al., 1988; Slominski et al., 2000; Busca and Ballotti, 2000). The eumelanogenic pathway is altered by agouti protein (AGP), via both functional antagonist of melanocortins and inverse agonist, which inhibits the expression and activity of melanogenesis-related proteins, melanogenic enzymes, and MC1-R, and thereby acts as a switch between eu- to pheomelanogenesis (Hearing, 1999; Barsh, et al., 2000; Wolff, 2003; Rouzaud et al., 2003). Also, note that the switch between pheo- to

572 eumelanogenesis in normal agouti is a discontinuous process, usually produced at low levels
573 of TYR activity (Oyehaug et al., 2002).

574 A recent report proposed on the role of p53, a key regulator agent for pigmentary
575 responses in tanning and pigmentation (Cui et al., 2007). Cui et al., proposed on the UV
576 induction of POMC including α-MSH and □-endorphin, which is directly controlled by p53,
577 and proposed that tanning from UVR is started by the activation of p53-mediated POMC
578 promoter (Cui et al., 2007). As illustrated in **Figure 2,** UV-induced DNA damage stabilizes the
579 tumor suppressor protein p53. However, this hypothesis is questionable since POMC knockout
580 C57BL/6 mice (the same strain used by Cui et al.,) possessed normal capability of melanin
581 pigment production (Slominski et al., 2004; Slominski et al., 2005a). This obtained result
582 decreases the strength of Cui's concept and also questions the validity of the proposed suntan
583 response and pathological hyperpigmentation (i.e., UV - p53 - POMC - melanin pigmentation).
584 Later, Slominski and their co-workers have published evidence to support the hypothesis that
585 it may not be POMC and its products, but rather the MC1-R that could be the key regulator of
586 pigmentation reported in mice (Slominski et al., 2007). On this background, we consider it
587 more likely that p53 acts as one important coordinator, but not the main or sole regulator of
588 pigmentation in the suntan response and pathological hyperpigmentation.

589 In case of the absence of POMC, it did not result in any changes in the melanogenesis,
590 when compared with the C57BL/6 mice measured using electron paramagnetic resonance
591 (EPR) spectroscopy, as well as morphologic and histological examinations. It is noted that the
592 eumelanogenic phenotype in C57BL/6 $POMC^{-/-}$ mice expresses MC1-R. Mutations in the
593 MC1R gene leads to fair skin in humans, which is also seen with inactivating human POMC
594 gene mutations. MC1R mutant receptor expression showed changes in the receptor activity,
595 which is also listed as one of the etiologic factors responsible for an increased incidence of
596 melanoma (Han et al., 2006; Rees, 2004). Therefore, these collated findings concluded that the

overwhelming dominance of POMC-derived peptides in the stimulation of melanogenesis, skin and hair pigmentation are complex in polygenic traits (Slominski et al., 2004).

1.9.2. *In-vitro* and clinical reports on melanogenesis

Slominski et al., reported on different methods to inhibit melanogenesis and showed immunosuppressive and mutagenic effect, which could alter the cellular metabolism. Melanin helps to protect against malignant melanocytes via chemo, radio, and photodynamic therapy and proposed to inhibit melanogenesis and also reduces the probability of melanoma progression (Slominski et al., 1998). Slominski et al., have studied its effect in human melanoma cells (SKMEL-188) by producing melanin pigment using tyrosine levels. The results showed that the pigmented melanoma cells were significantly less sensitive to cyclophosphamide and also kills the action of IL-2-activated peripheral blood lymphocytes. This inhibition of melanogenesis can be achieved either by blocking TYR site or chelating Cu ions to the cytotoxic action of cyclophosphamide towards melanoma cells, and also activates the IL-2 in the lymphocytes. The exogenous L-DOPA inhibits the proliferation of lymphocyte causing cell cycle arrest in G1/0 phase and also inhibits the production of IL-1□, TNF-α, IL-6 and IL-10, respectively. Thus, the cytotoxic action of cyclophosphamide could not impair the active melanogenesis, but it also possesses immunosuppressive activity. Therefore, this resistance to a chemotherapeutic or immunotoxic activity of lymphocytes could be reversed by TYR inhibitors (Slominski et al., 2009). In another study by Slominski et al., showed to inhibit the behaviour of melanogenesis in regulation with melanoma by altering the expression of HIF-1α and its related pathways. The study was carried out using human (SKMEL-188) and hamster (AbC1) melanoma cells for their activity using cell culture methods. The results showed to significantly increase the melanin pigmentation of HIF-1α, in both the cells. In cultured cells, the result on melanogenesis were significantly stimulated by the expression of HIF-1-dependent target genes that play an important role in angiogenesis and cellular metabolism.

Therefore, they have concluded that induction of melanogenic pathway could lead to elevated HIF-1-dependent and independent pathways in cultured melanoma cells, suggesting a key role for the regulation of cellular metabolism in melanogenesis (Slominski et al., 2014).

Brożyna et al., reported the effects and survival of melanogenesis in patients with stage III and IV melanoma. The samples were collected from American Joint Committee in 20 patients from stage I, 24 patients from stage II, and 29 patients from stage III cancers and the results were analysed by Prof Franciszek Łukaszczyk Memorial Hospital, Oncology Centre, Bydgoszcz, Poland. The results showed that the patients with metastatic disease, and those with melanomas exhibit significant disease-free survival than those with amelanotic lesions. Thus, melanogenesis shortens overall survival in patients with metastatic melanoma. Therefore, the authors concluded that inhibiting the process of melanogenesis appears to be an interesting approach for the treatment of metastatic melanoma (Brożyna et al., 2013). In another study by Brożyna et al., studied the activity of melanin content in metastases melanoma and its effect in radiotherapy using cohort study with two melanoma patients that were diagnosed and treated at the Oncology Centre in Bydgoszcz, Poland. The study results showed significant decrease in the melanin pigmentation in pT3 and pT4 melanomas in comparison to pT1 and pT2 tumors, respectively. However, melanin levels were measured in pT3-pT4 melanomas developing metastases stage (pN1-3, pM1) were found to be higher in pN0 and pM0 cases. Therefore, the results concluded that the presence of melanin in metastatic melanoma cells decreases the outcome of radiotherapy, and melanin synthesis that is related to higher disease advancement (Brożyna et al., 2016). Based on our cell-based and clinical research and present research we also suggest that inhibition of melanogenesis can improve radiotherapy modalities.

1.10. Discussion and Conclusion

Progress in the treatment of melanoma begins with identifying a specific target involved in the melanoma pathogenesis, and one such interesting target is by altering the TYR enzyme

(Hodi et al., 2010). The use of pro-drugs could also be a newer and interesting approach in the treatment of melanoma, but it tends to form toxic metabolites and thus requires alternative therapy (Rooseboom et al., 2004; Gasowska-Bajger and Wojtasek, 2008; Jawaid et al., 2009). Therefore, given that TYR reported to have a pivotal activity as a natural photo-protection of the skin, where several intrinsic and extrinsic factors that could influence its function, and it is also critical to understand the precise mechanisms of onset and progression of melanoma. While the etiological aspect is still unclear, were still it is believed that the DNA damage in the melanocyte is the leading cause of melanocyte's transformation and progression to melanoma.

The UVR from sun is one of the primary ecological reasons in the development of melanoma, which proliferates due to UVR -induced DNA mutations that occur in skin. The UV plays an important role in the brain and central neuroendocrine system in order to reset body homeostasis (Slominski et al., 2018; Skobowiat et al., 2011). Also, Slominski and their co-workers stated that melanoma can affect some central neuroendocrine axes and how cancer hijacks the body's homeostasis through the neuroendocrine system (Slominski et al., 2023). The epidermal melanocytes, are pigment producing cells of neural crest origin that communicates with multiple targets. Therefore, alterations in the epidermal melanocytes can affect the cutaneous functions (Slominski et al., 1993). Therefore, this leads to the activation of POMC and release of MSH from the keratinocytes, and increases the cAMP levels, which further activates the MITF transcription (Cui et al., 2007; Garibyan and Fisher, 2010). This results in the synthesis of melanin from TYR and protects from DNA damage. In keratinocytes, exposure of UVR activates NOS type 1, which leads to increased nitric oxide and TYR levels and subsequent acceleration of melanogenesis and also elevates the cofactors such as NADPH and 6-BH4 (Roméro-Graillet et al., 1997). Later on, Cannon-Albright et al., reported that exposure to UVR in patient with "9p-linked" gene were altered, which further gives us hint that mutations may also occur due to hereditary reason. The most commonly identified mutations

672 in melanoma are *CDKN2A* and CDK4, where mutations in the *CDKN2A* gene results in a
673 defective p14 and p16, which is stabilized by p53 (Mehnert and Kluger, 2012). Davis et al.,
674 reported that mutations in the NER pathway could develop the risk of melanoma and showed
675 that NER pathways increase the UVR-induced unrepaired DNA damage (Davis et al., 2019).
676 There are other signalling pathways such as *BRAF, NRAS, NF1, PTEN, TP53, TERT, ARID2*
677 and *MAPK*, which also showed in altering these genes that are associated with melanoma.
678 TYR is a rate-limiting step in the melanin production, where it catalyses L-tyrosine to
679 L-DOPA. Thus, it could be targeted to inhibit the irregular melanin synthesis and the
680 pathogenesis of melanoma (Buitrago et al., 2016; Pillaiyar et al., 2017; Van Staden et al., 2021).
681 Slominski et al., reported that both L-tyrosine and L-DOPA, serves as an intermediate for
682 melanogenesis, and acts as bioregulatory agents that helps to regulate the cellular functions
683 (Slominski and Paus, 1990; Slominski et al., 2012). The TYR catalyses via three distinct
684 melanogenic pathways i.e., hydroxylation of L-tyrosine, dehydrogenation of L-DOPA, and
685 dehydrogenation of DHI, which involves exchange of electrons with copper atoms that
686 generates orthoquinone and water as final products (Slominski et al., 2004). The TYR is
687 expressed in two forms of protein TYRP1 and TYRP2. Defects in the TYR gene leads to a
688 condition called negative oculocutaneous albinism type 1 (OCA1) (Tomita et al., 1989; Takeda
689 et al., 1990; Oetting and King, 1999). Thus, in oculocutaneous albinism type 3 (OCA3), the
690 TYRP1 is mutated within the ER and the normal processing of TYR is terminated leading to
691 proteasomal degradation and thus reduces pigmentation (Kushimoto et al., 2003; Toyofuku et
692 al., 2001a; Toyofuku et al., 2001b). In case of oculocutaneous albinism type 2 (OCA2) and
693 type 4 (OCA4), the TYR from trans-Golgi Network (TGN) to melanosomes is disrupted (Chen
694 et al., 2002; Toyofuku et al., 2002; Costin et al., 2003; Kushimoto et al., 2003). Therefore, the
695 experimental evidence in melanocytes targeting melanosomes, shows that ER is an essential
696 step for TYR maturation, which is important in the production of melanin pigments (Halaban,

2000; Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Halaban et al., 1997; Halaban et al., 2000). Thus, defects in OCA1 via OCA4 shows melanogenic activity *in-vivo*, via posttranslational pathways, which is an important step in the processing of TYR. The MITF transcription factor regulates the MRGE expression in cultured melanoma, and showed to increase the glycosylation of TYR in the ER, which results in pigmentation (Imokawa, 1989). In TYR, the ERAD is regulated by ubiquitin-proteasome system, E3 ligases Doa10p and Hrd1p, which results in degradation (Hammond and Helenius, 1995; Bordallo et al., 1998). Thus, mutations in TYR result in TYR sequestration in the ER and is degraded through ERAD by inhibiting its functions (Smith et al., 2004). Therefore, ER plays a significant role in the regulation of TYR. Our review collated that various approaches to regulate the abrupt melanogenesis in melanoma and could modulate the TYR enzyme levels or activity. However, the clinical safety of TYR modulators in both acute and long-term use is an evolving area of research focus in the fields of skin cancer therapeutics.

As we discussed, the POMC is regulated by CRH, which affects the functions of melanocytes and melanoma cells (Slominski et al., 2013). The regulation process by external agents such as α-MSH and its antagonist agouti, are both mediated by the MC1-R at the surface of the melanocyte. A mathematical model is developed to improve our understanding of melanogenic switching, i.e., agouti background, which acts as a switch between eumelanin and pheomelanin production depending on the extracellular signaling context (Oyehaug et al., 2002).

As reviewed, selective findings have provided intriguing leads and that warrant further research and a clear understanding of the critical roles of TYR in cell signaling pathways controlling melanogenesis. Delineation of these leads may unravel new therapeutic targets to treat melanin-related pigmentary disorders and melanoma. Nonetheless, our review collates that the TYR enzyme exhibits a critical role in paving melanoma's pathogenesis and is a

potential druggable target to combat melanoma. However, the quest to unravel the clinically safe TYR modulators remains elusive.

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Author Contribution

Rajan Logesh - Conceptualization; **Rajan Logesh, Sagar Rajendra Prasad** - Data curation; Writing - review & editing; **Nirmal Robinson** - Methodology; **Sandhya Chipurupalli** - Software; **Nirmal Robinson** and **Suresh Kumar Mohankumar** – Supervision.

Conflict of Interest

The authors declare no competing financial interest.

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Figure Captions

Fig. 1. Risk factors of melanoma. UV radiation is the major environmental factor affecting melanoma. Other risk factors include skin phenotype, number of naevi and chemical pollutants like arsenic; Germ-line mutations in genes regulating cell cycle arrest & DNA repair mechanism; Somatic mutations in pathways regulating cell proliferation, growth & metabolism, and oncogenic signalling.

Fig. 2. Role of Tyrosinase in melanin synthesis: Conversion of L-tyrosine to L-DOPA is the rate-limiting step in melanin synthesis, and this step is catalyzed by the enzyme Tyrosinase. It further converts L-DOPAse to DOPA-quinone, which in turn follows a sequence of steps catalyzed by Tyrosinase and forms DHI Melanin (Black), DHICA Melanin (Brown). In the presence of cysteine or glutathione, DOPA-quinone is sequentially converted to Pheomelanin

(Yellow to Red) which is independent of Tyrosinase. The region highlighted in orange colour shows the steps catalysed by Tyrosinase.

Table Captions

Table 1. List of components inhibiting the TYR expression level.

Table 2. List of reported phytochemicals showing Tyrosinase inhibitory activity with their IC_{50} values.

Table 3. List of reported medicinal plant's showing Tyrosinase inhibitory activity with their IC_{50} values.

Response to editor and reviewers

Manuscript Title: "Natural Tyrosinase Enzyme Inhibitors: A path from melanin to melanoma and its reported pharmacological activities".

Manuscript ID: BBACAN-D-23-00029R3

Reviewer #1: The manuscript still requires minor revisions.

Rev: I recommend careful proof-reading of next version prior submission

Res: Thank you so much for your comment. The entire manuscript has been proof-read in the revised manuscript.

Rev: Fig. 1 is missing

Res: Thank you for your comment. The figure 1 has been included in the revised manuscript.

Rev: Lines 42 and 43 (abstract): it should be plural: are found to be important regulators for pigmentation.

Res: Thank you so much for your comment. The sentence has been changed to plural form in the revised manuscript.

Rev: Make sure that for alpha-MSH, beta-endorphin you use Greek symbols! For example on line 568

Res: Thank you so much for your comment. I have checked with the previously submitted manuscript, we have already used Greek symbols in the revised manuscript.

Rev: Lines 464 and 465, there are miss-citations: replace Paus et al, with two reviews on CRH signaling in FASEB J 15, 1678-1693, 2001 and Endocrine Rev 34:827-884, 2013

Res: Thank you so much for your suggestion. The two references has been cited in the revised manuscript.

Rev: Line 704 - this is not C57BL/7 mouse, because it is aa. To switch it has to be agouti background. Please correct.

Res: Thank you so much for your comment. The changes have been addressed in the revised manuscript.

Rev: line 476-478: Please correct, It is well established than CRH at the systemic level regulates corticosterone. Please correct and cite Chrousos review

Res: Thank you so much for your suggestion. The sentence has been corrected and the Chrousos manuscript has been cited in the revised manuscript.

Reviewer #2: Dear Authors

Rev: Thank you for addressing my comments.

Res: Thank you so much for your response.

HIGHLIGHTS

- Melanoma is a major concern among the Caucasian population and its incidence is increasing globally.
- UV radiation is the major environmental risk factor for the induct and progression of melanoma.
- Melanin defends the skin against UV-induced DNA damage and genetic changes thus inhibits melanoma formation.
- Tyrosinase is a key catalytic enzyme regulating melanin production and has significant part in the pathogenesis of melanoma.
- The medicinal plants and molecules have the potential to modulate tyrosinase enzyme possibly emerge as a viable therapeutic option to combat melanoma.
- The clinical studies on the novel drugs targeting tyrosinase enzymes are limited but continue to prospects in the next generation melanoma therapeutics discovery.
- The in-depth review on tyrosinase provides the deeper insights on the critical roles and molecular dynamics of tyrosinase in a path from melanin to melanoma.

Graphical Abstract

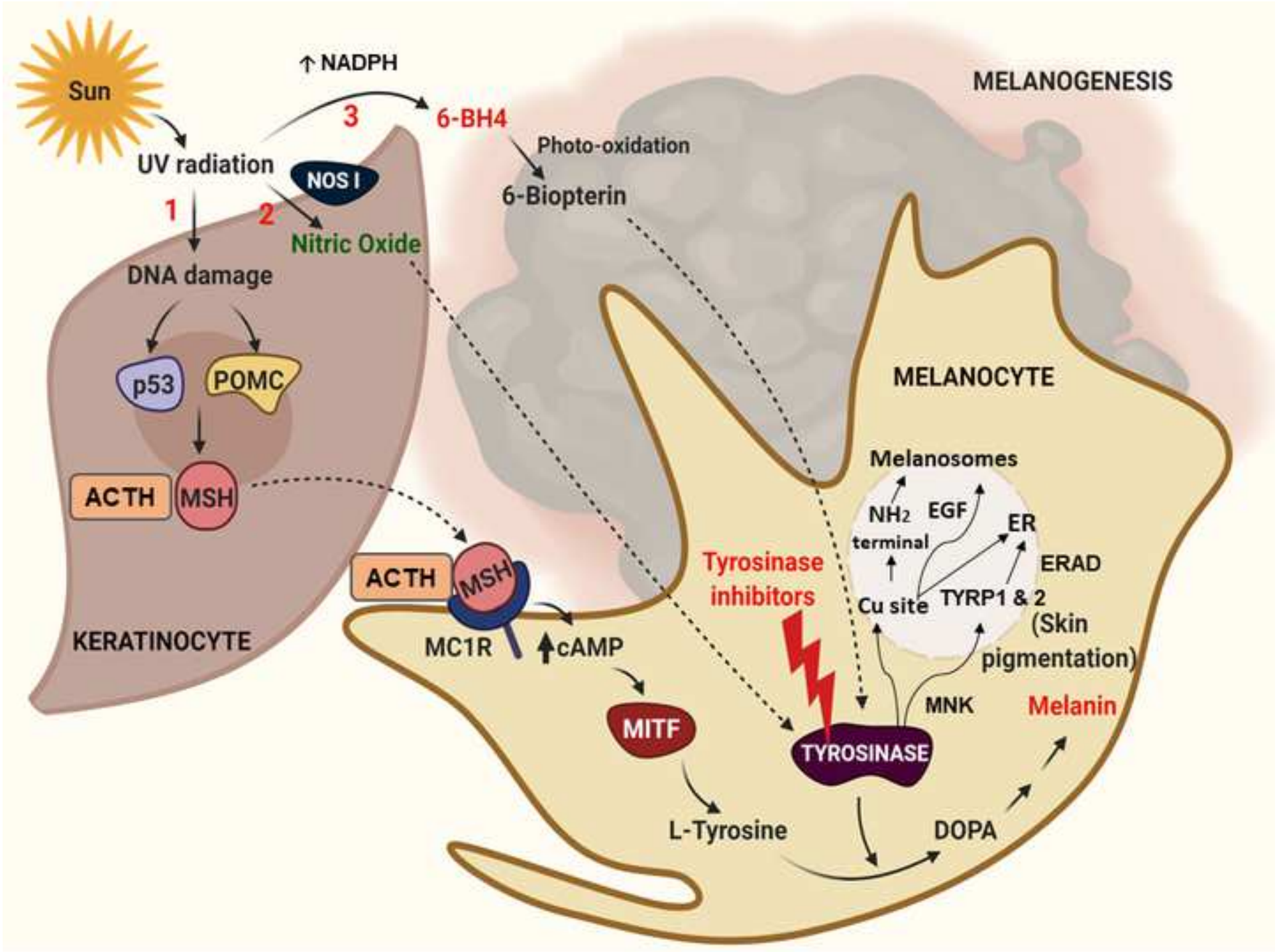
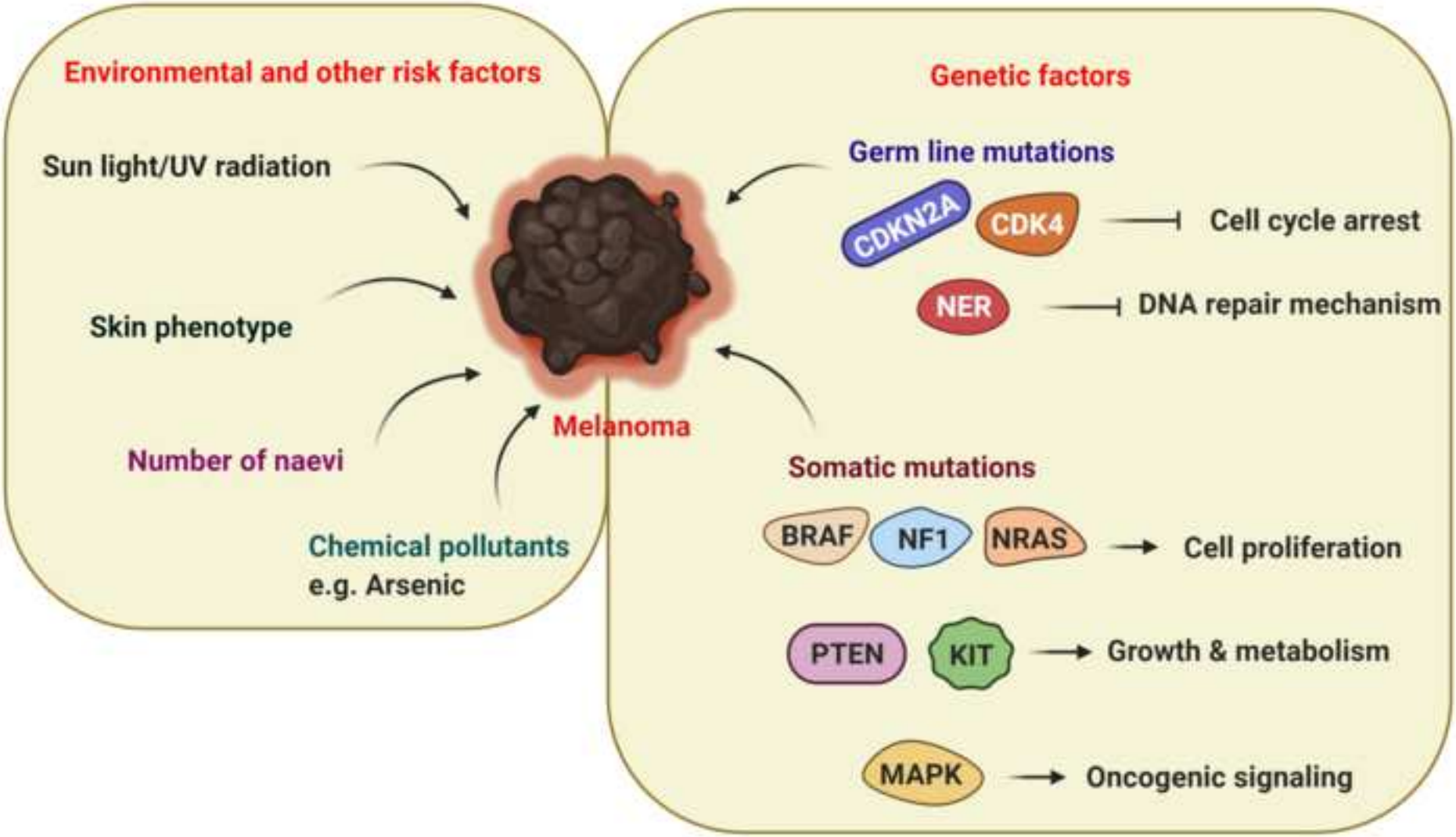
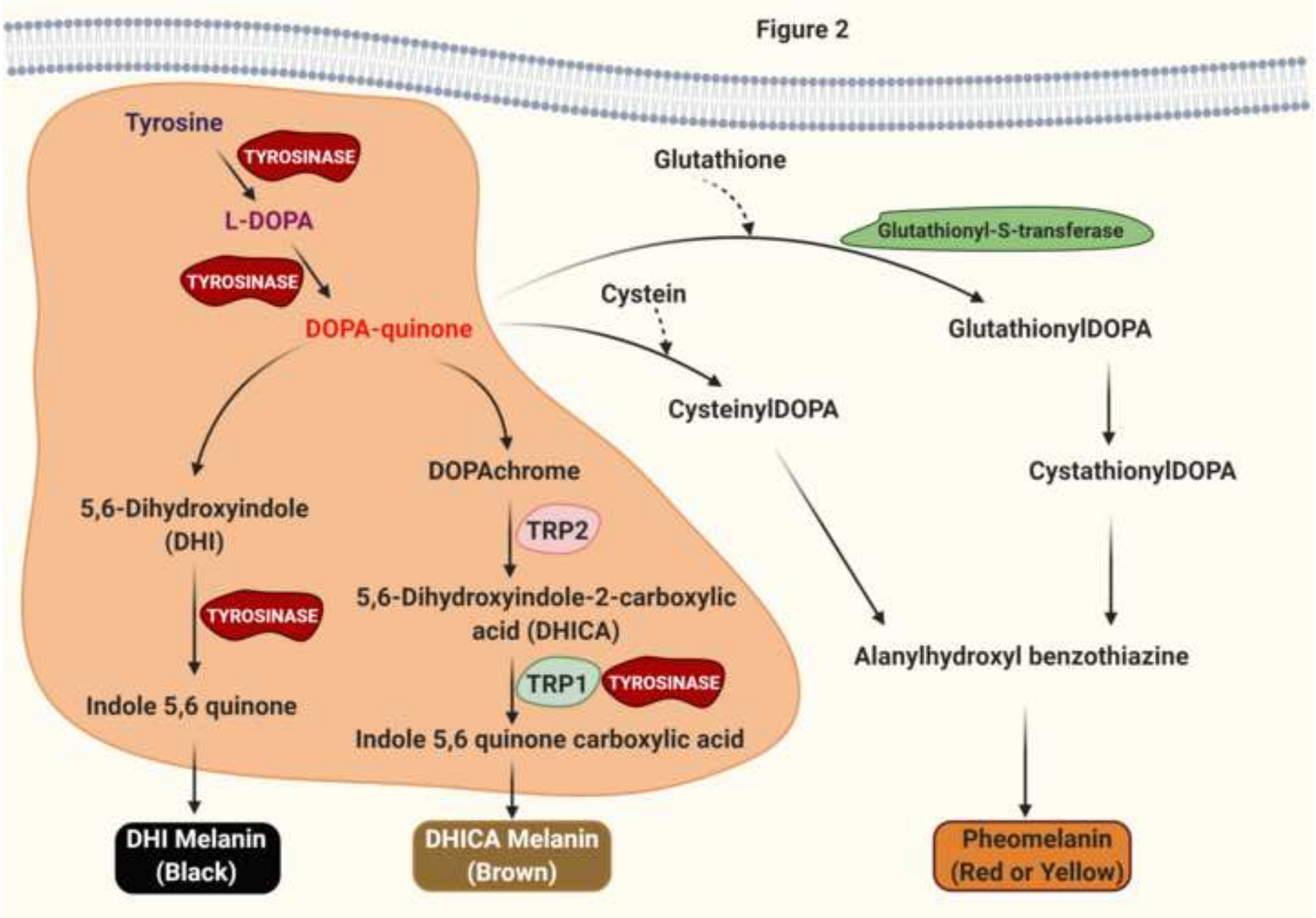


Figure 1



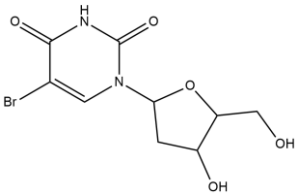
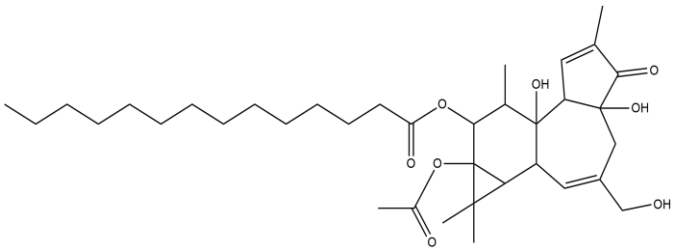
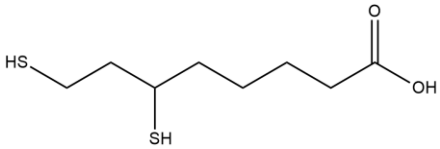
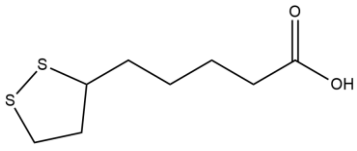
Figure

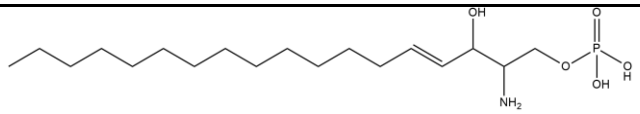
Click here to access/download;Figure;Figure 2.png



Tables

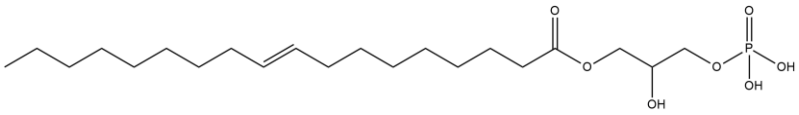
Table 1. List of components inhibiting the Tyr expression level.

S.No	Components	Reference
Mechanism: Inhibiting the mRNA transcription of Tyr enzyme		
1	5-Bromodeoxyuridine  (Pubchem CID: 6035)	Kidson and De Haan, 1990
2	12-O-Tetradecanoylphorbol-13-acetate  (Pubchem CID: 27924)	Toyofuku et al., 2001a
3	Dihydrolipoic acid  (Pubchem CID: 421)	Toyofuku et al., 2001b
4	Lipoic acid  (Pubchem CID: 6112)	Toyofuku et al., 2001b
5	Sphingosine-1-phosphate	Kim et al., 2003



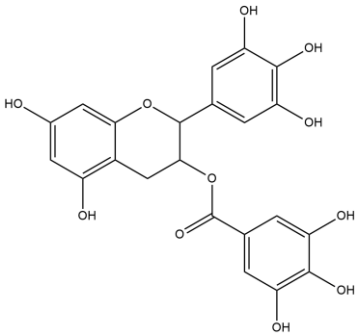
(Pubchem CID: 5283560)

6	Lysophosphatidic acid	(Kim et al., 2004a)



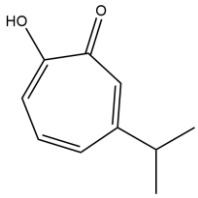
(Pubchem CID: 5497152)

7	(-)-Epigallocatechin-3-gallate	(Kim et al., 2004b)



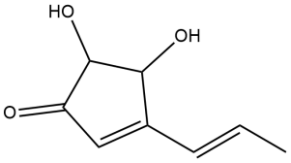
(Pubchem CID: 65064)

8	Hinokitiol	(Kim et al., 2004b)



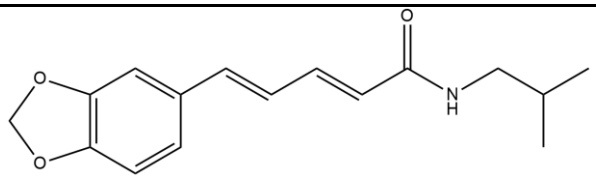
(Pubchem CID: 3611)

9	Terrein	(Park et al., 2004)

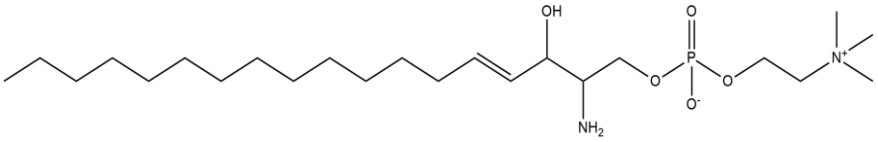
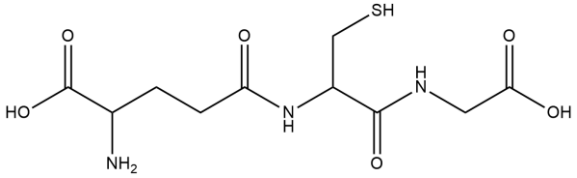
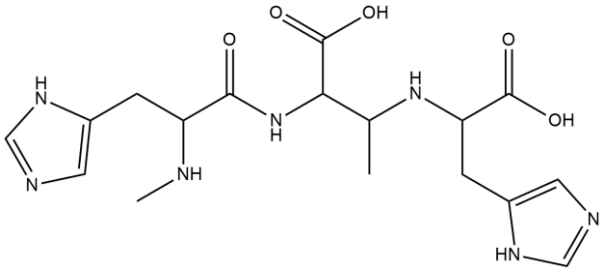
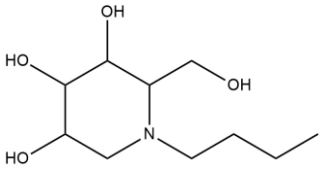


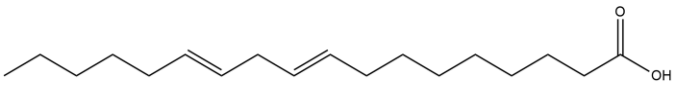
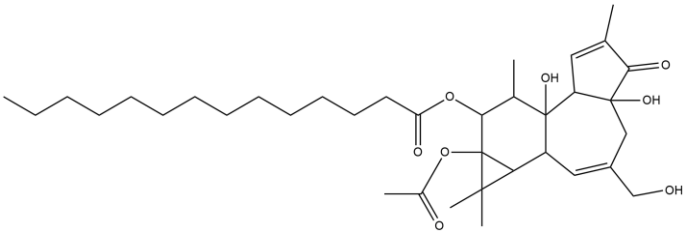
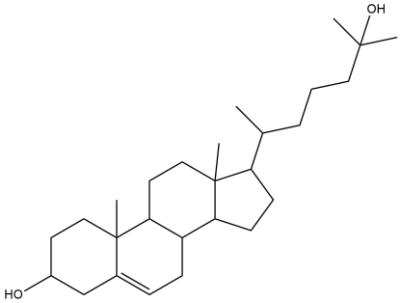
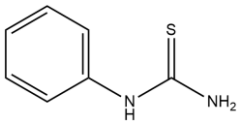
(Pubchem CID: 6436830)

10	Piperlonguminine	(Kim et al., 2006a)



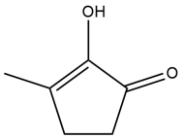
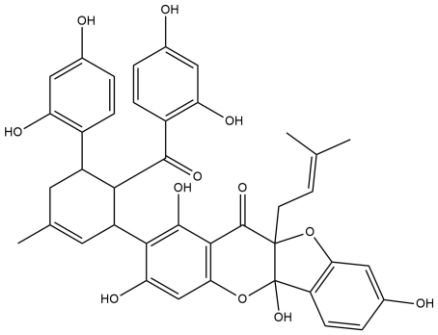
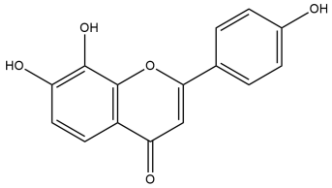
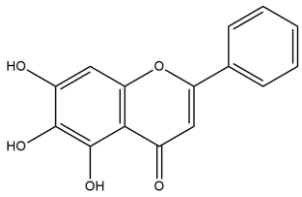
(Pubchem CID: 5320621)

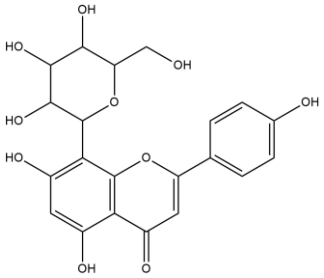
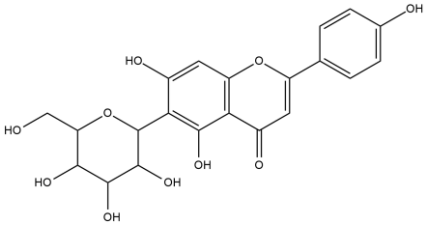
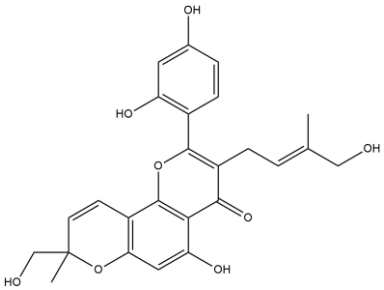
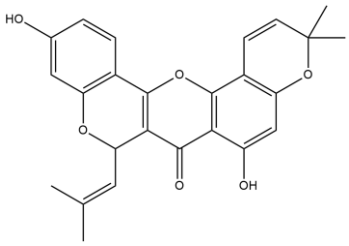
11	Sphingosylphosphorylcholine  (Pubchem CID: 9847290)	(Kim et al., 2006b)
	Mechanism: Aberrant Tyr maturation	
12	Glutathione  (Pubchem CID: 124886)	(Bhatnagar et al., 1993)
13	Feldamycin  (Pubchem CID: 10409115)	(Raposo et al., 2001)
14	N-Butyldeoxynojirimycin  (Pubchem CID: 51634)	(Tucker and Goldstein, 2003)

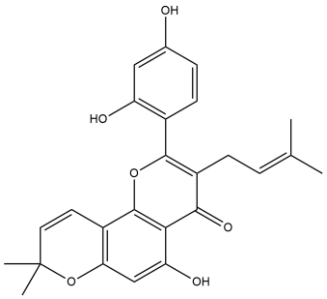
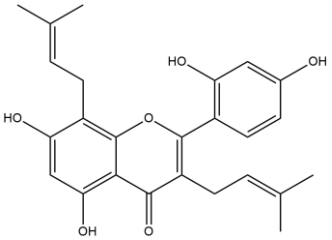
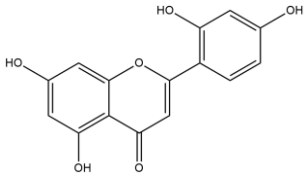
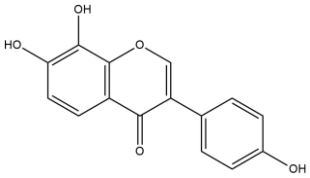
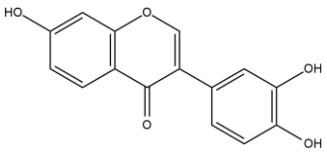
Mechanism: Acceleration of Tyr degradation		
15	Linoleic acid  (Pubchem CID: 5280450)	(Ando et al., 1999)
16	2,20-Dihydroxy-5,50-dipropyl-biphenyl (Pubchem CID: SNA)	(Nakamura et al., 2003)
17	12-O-Tetradecanoylphorbol-13-acetate  (Pubchem CID: 27924)	(Kageyama et al., 2004)
18	Phospholipase D2 (Pubchem CID: SNA)	(Kageyama et al., 2004)
19	25-Hydroxycholesterol  (Pubchem CID: 65094)	(Hall et al., 2004)
20	Phenylthiourea  (Pubchem CID: 676454)	(Hall and Orlow, 2005)

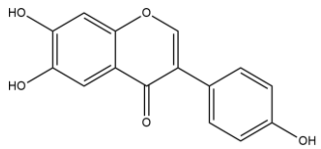
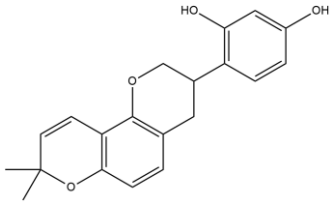
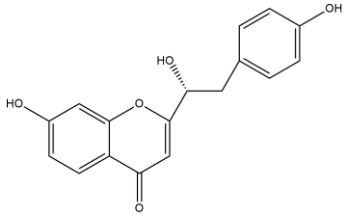
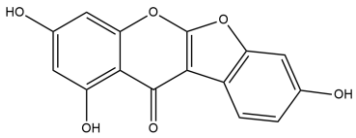
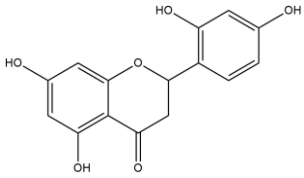
*SNA-Structure not available

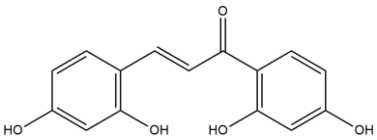
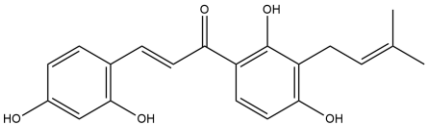
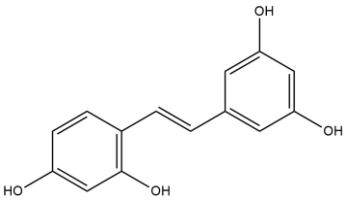
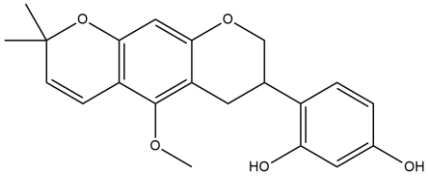
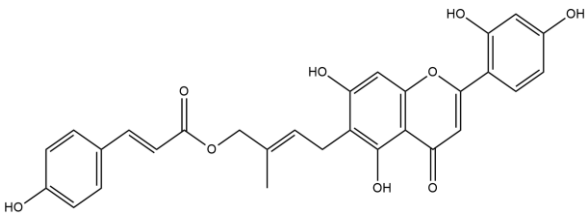
Table 2. List of reported phytochemicals showing Tyrosinase inhibitory activity with their IC_{50} values.

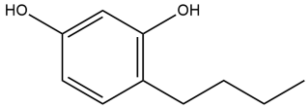
Sl. no	Compound Name	Plant/Extract/ Mode of Inhibition	IC_{50} value	References
1	2-hydroxy-3methylcyclopent-2-enone  (Pubchem CID: 6660)	NM; (M)	721.91mg/mL	(Hwang et al., 2018)
2	3',5'di-C-b glucopyranosylphloretin (SNA)	Calamondin peel; Water (C)	0.87mg/ml	(Lou et al., 2012)
3	Sanggenon D  (Pubchem CID: 13824422)	Morus mongolica; (NC)	7.3µM	(Lee et al., 2004)
4	7,8,4'-trihydroxyflavone  (Pubchem CID: 688853)	NM; (M)	10.31±0.41µM	(Shang et al., 2018)
5	Baicalein 	NM; (NC)	0.11 mM	(Guo et al., 2018; Zhang et al., 2021)

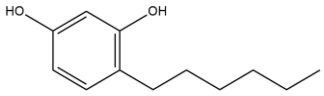
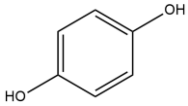
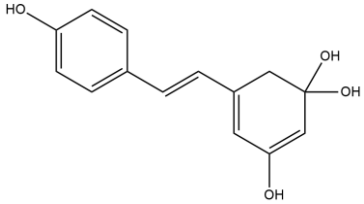
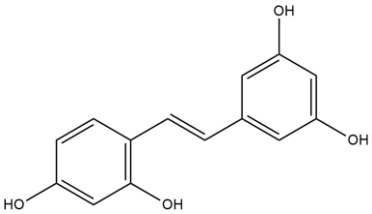
	(Pubchem CID: 5281605)			
6	Vitexin  (Pubchem CID: 5280441)	Vigna radiatae; EtOH (M)	6.3mg/ml	(Yao et al., 2012)
7	Isovitexin  (Pubchem CID: 162350)	Vigna radiatae; EtOH (M)	5.6mg/ml	(Yao et al., 2012)
8	Mormin  (Pubchem CID: 54587663)	Morus lhou; MeOH (C)	0.088mM	(Ryu et al., 2008)
9	Cyclomorusin  (Pubchem CID: 5481969)	Morus lhou; MeOH (C)	0.092mM	(Ryu et al., 2008)
10	Morusin	Morus lhou; MeOH (C)	0.250mM	(Ryu et al., 2008)

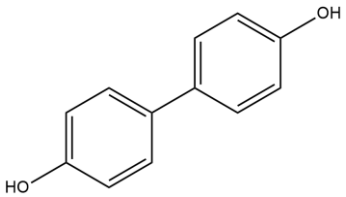
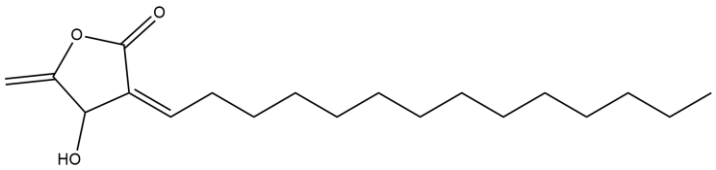
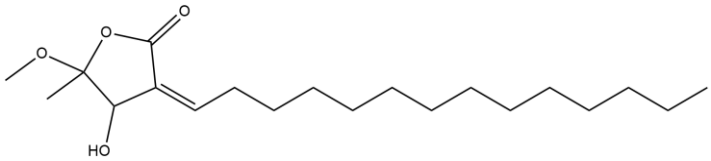
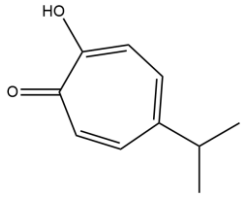
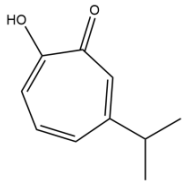
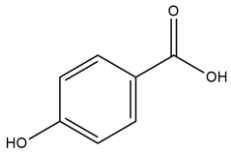
	 (Pubchem CID: 5281671)			
11	Kuwanon C  (Pubchem CID: 5481958)	Morus lhou; MeOH (C)	0.135mM	(Ryu et al., 2008)
12	Norartocarpetin  (Pubchem CID: 5481970)	Morus lhou; MeOH (C)	1.2 µM	(Ryu et al., 2008)
13	7,8,4’-trihydroxyisoflavone  (Pubchem CID: 5466139)	Soybean; (NM)	11.21±0.8µM	(Park et al., 2010)
14	7,3’,4’-trihydroxyisoflavone  (Pubchem CID: 5284648)	Soybean; (NM)	5.23±0.6µM	(Park et al., 2010)
15	6,7,4’-trihydroxyisoflavone	NM; (C)	9.2µM	(Chang et al., 2005)

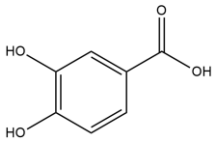
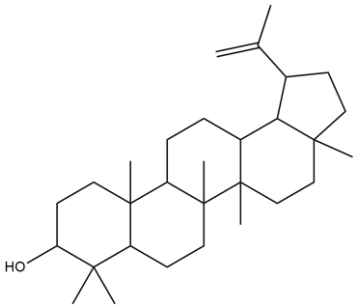
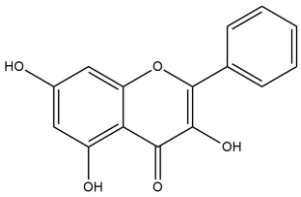
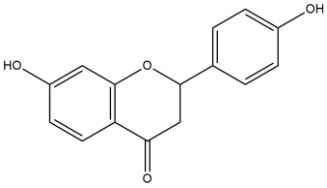
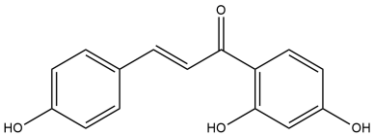
	 (Pubchem CID: 5284649)			
16	Glabridin  (Pubchem CID: 124052)	Glycyrrhiza glabra; (NC)	0.43µM	(Chen et al., 2016)
17	Mirkoin  (Pubchem CID: SNA)	Maackia fauriei; EtOH 70% (NC)	5µM	(Kim et al., 2010)
18	Lupinalbin A  (Pubchem CID: 5324349)	Apios americana; MeOH (C)	39.7±1.5µM	(Kim et al., 2018)
19	20-hydroxygenistein-7-O-gentibioside (SNA) (Pubchem CID: NA)	Apios americana; MeOH (C)	50.0±3.7µM	(Kim et al., 2018)
20	Steppogenin  (Pubchem CID: 21596130)	Morus alba; EtOH 70% (C)	0.98±0.01µM	(Zhang et al., 2016)
21	2,2’,4,4’-tetrahydroxychalcone	Morus alba; EtOH 70% (C)	0.07±0.02µM	(Zhang et al., 2016)

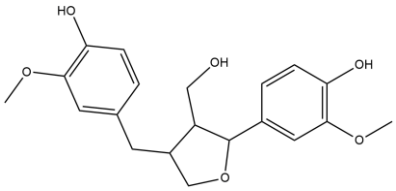
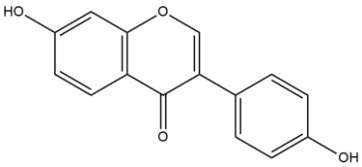
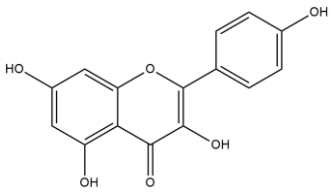
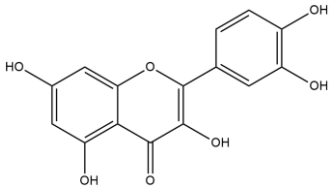
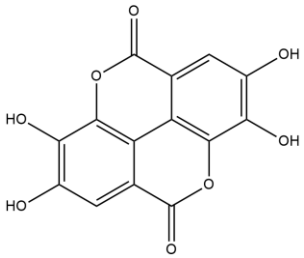
	 (Pubchem CID: 10107266)			
22	Morachalcone A  (Pubchem CID: 9862769)	Morus alba; EtOH 70% (C)	0.08±0.02µM	(Zhang et al., 2016)
23	Macrourins E (SNA) (Pubchem CID: NA)	Morus macroura; EtOH (NM)	0.39µM	(Wang et al., 2018)
24	Oxyresveratrol (*Morus alba*)  (Pubchem CID: 5281717)	Morus alba; EtOH 70% (C)	0.10±0.01	(Zhang et al., 2016)
25	Neorauflavane  (Pubchem CID: 44257517)	Campylotropis hirtella; MeOH (C)	30 nM	(Tan et al., 2016)
26	Artocaepin E  (Pubchem CID: 132915900)	*Artocarpus heterophyllous;* MeOH Extract (C)	6.7 ± 0.8 µM	(Nguyen et al., 2016)
27	Artocaepin F	*Artocarpus*	>50 µM	(Nguyen et

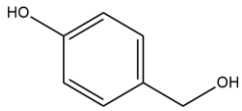
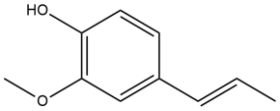
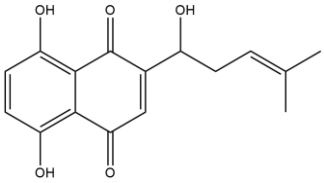
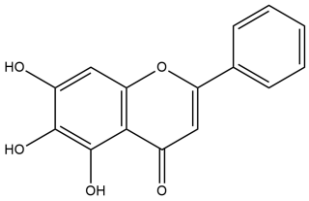
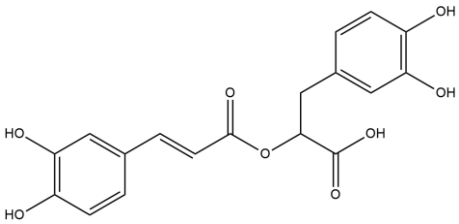
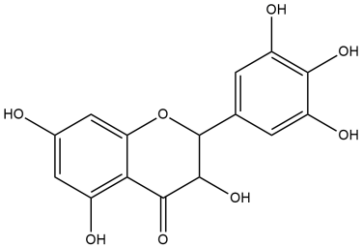
		heterophyllous;		al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
28	Orartocarpetin	*Artocarpus heterophyllous;*	>50 μM	(Nguyen et al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
29	Artocarpanone	*Artocarpus heterophyllous;*	2.0 ± 0.1 μM	(Nguyen et al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
30	Liquiritigenin	*Artocarpus heterophyllous;*	22.0 ± 2.5 μM	(Nguyen et al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
31	Steppogenin	*Artocarpus heterophyllous;*	7.5 ± 0.5 μM	(Nguyen et al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
32	Dihydromorin	*Artocarpus heterophyllous;*	>50 μM	(Nguyen et al., 2016)
	(Pubchem CID:)	MeOH Extract (C)		
33	4-butylresorcinol  (Pubchem CID: 205912)	(C)	13.5 & 21 μM	(Kolbe et al., 2013; Mann et al., 2018)
34	Thiamidol (SNA) (Pubchem CID: NA)	(C)	1.1 μM	(Mann et al., 2018)
35	4-hexylresorcinol	(C)	94 μM	(Mann et al.,

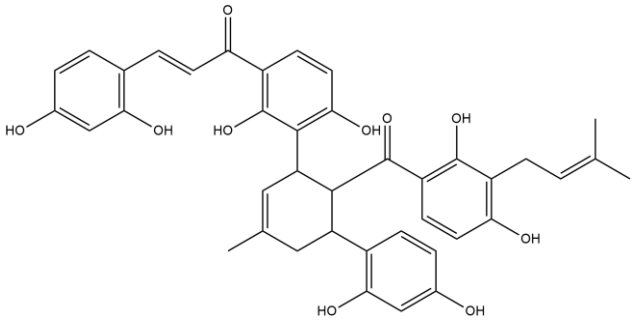
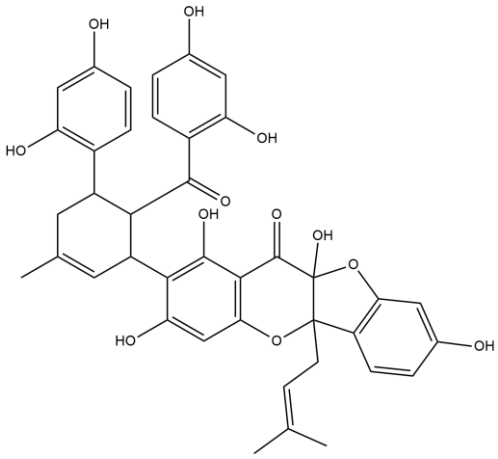
	 (Pubchem CID: 3610)			2018)
36	4-phenylethylresorcinol (SNA) (Pubchem CID: NA)	NM; (C)	131 μM	(Mann et al., 2018)
37	Hydroquinone  (Pubchem CID: 785)	NM; (C)	15 μM	(Mann et al., 2018)
38	2,4,3′-trihydroxydihydrostilbene (SNA) (Pubchem CID: NA)	Morus alba wood; MeOH Extract (NM)	0.8 ± 0.15 μM	(Chaita et al., 2017)
39	Dihydrooxyresveratrol  (Pubchem CID: 129650478)	Morus alba wood; MeOH Extract (NM)	0.3 ± 0.05 μM	(Chaita et al., 2017)
40	Oxyresveratrol  (Pubchem CID: 5281717)	Morus alba wood; MeOH Extract (NM)	1.7 μM	(Chaita et al., 2017)
41	Benzofuran moracin M (SNA) (Pubchem CID: NA)	Morus alba wood; MeOH Extract (NM)	8.0 μM	(Chaita et al., 2017)
42	4,4′-dihydroxybiphenyl	NM; (C)	1.91 μM	(Kim et al.,

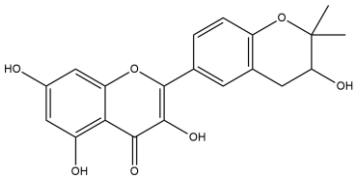
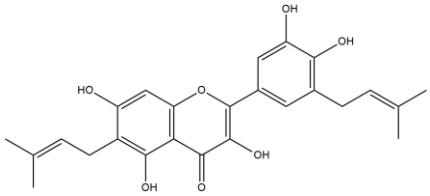
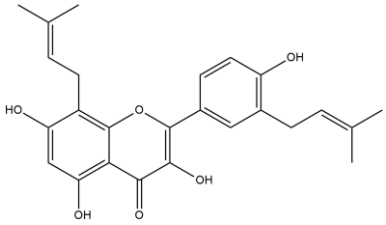
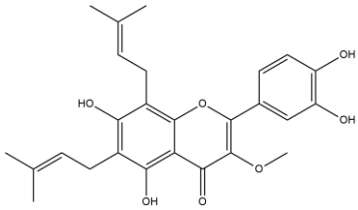
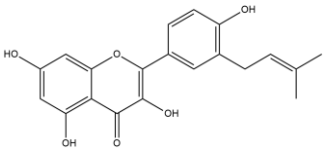
				2005)
	(Pubchem CID: 7112)			
43	Linderanolide B	Cinnamomum subavenium; MeOH (NA)	1 μM	(Wang et al., 2011)
				
	(Pubchem CID: 53308122)			
44	Subamolide A	Cinnamomum subavenium; MeOH (NA)	1 μM	(Wang et al., 2011)
				
	(Pubchem CID: 16104909)			
45	γ-thujaplicin	NM; (C)	1.15 μM	(Yoshimori et al., 2014)
				
	(Pubchem CID: 12649)			
46	β-thujaplicin	NM; (C)	8.98 μM	(Yoshimori et al., 2014)
				
	(Pubchem CID: 3611)			
47	p-hydroxybenzoic acid	Vitex agnus-castus; (NM)	16.97 μM	(Azizuddin et al., 2011)
				

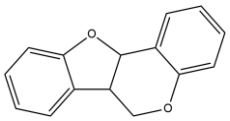
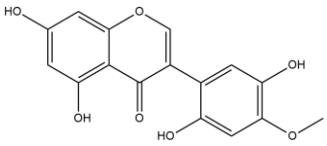
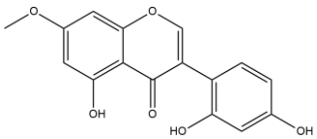
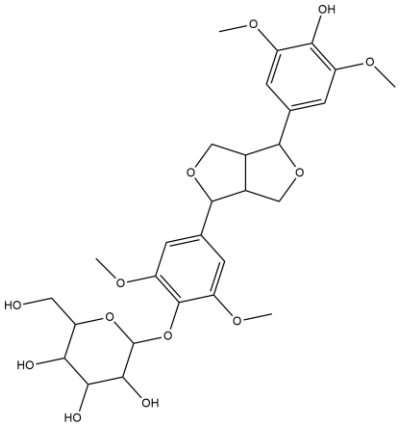
	(Pubchem CID: 135)			
48	3,4-dihydroxybenzoic acid  (Pubchem CID: 72)	Vitex agnus-castus; (NM)	66.67 μM	(Azizuddin et al., 2011)
49	Lupeol  (Pubchem CID: 259846)	Tannacetum polycephalum; (NM)	27.40 μM	(Azizuddin et al., 2011)
50	Galangin  (Pubchem CID: 5281616)	Alpinia officinarum; (NM)	3.55 μM	(Chung et al., 2018)
51	Liquiritigenin  (Pubchem CID: 114829)	Pueraria lobata; MeOH Extract (NM)	25.24 ± 6.79 mM	(Morgan et al., 2016)
52	Isoliquiritigenin  (Pubchem CID: 638278)	Pueraria lobata; MeOH Extract (NM)	4.85 ± 2.29 mM	(Morgan et al., 2016)
53	Lariciresinol	Pueraria	21.49 ± 4.44	(Morgan et

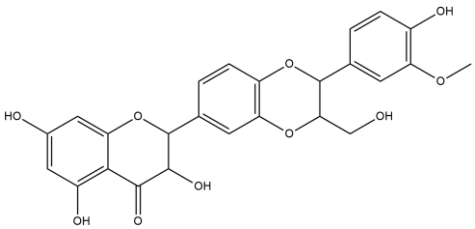
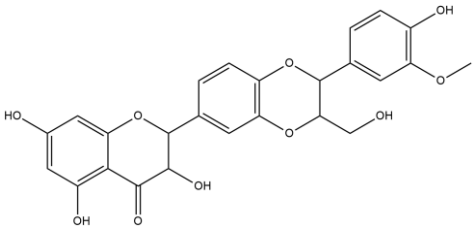
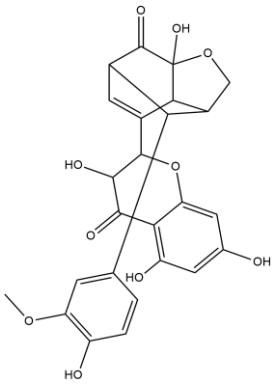
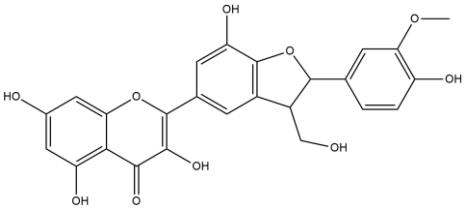
	 (Pubchem CID: 332427)	lobata; MeOH Extract (NM)		al., 2016)
54	Daidzein  (Pubchem CID: 5281708)	Pueraria lobata; MeOH Extract (NM)	17.5 ± 1.29 mM	(Morgan et al., 2016; El-Nashar et al., 2021)
55	Kaempferol  (Pubchem CID: 5280863)	R. damascena; MeOH Extract (C)	1.58 ± 0.18 µg/ml	(Solimine et al., 2016)
56	Quercetin  (Pubchem CID: 5280343)	R. damascena; MeOH Extract (C)	1.27 ± 0.06 µg/ml	(Solimine et al., 2016)
57	Ellagic acid  (Pubchem CID: 5281855)	R. damascena; MeOH Extract (M)	1.58 ± 0.09 µg/ml	(Solimine et al., 2016)
58	4-hydroxybenzylalcohol	Sinapis alba; MeOH:Water (NM)	6 µM	(Popova et al., 2018)

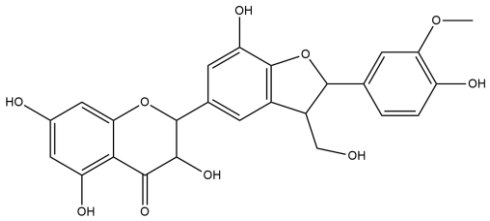
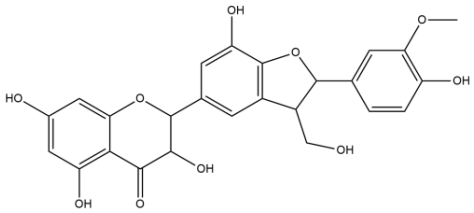
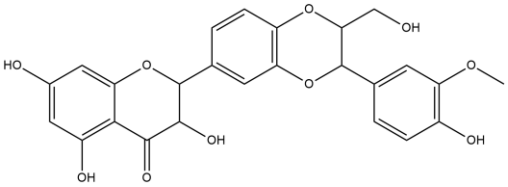
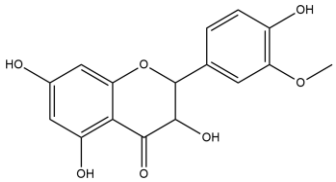
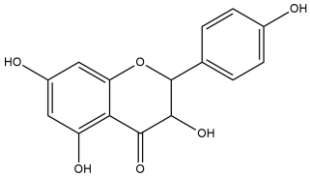
	 (Pubchem CID: 125)			
59	Isoeugenol  (Pubchem CID: 853433)	NM; (C)	33.3 μmol/L	(Zuo et al., 2018)
60	Shikonin  (Pubchem CID: 479503)	NM; (C, UC, M)	26.67 μmol/L	(Zuo et al., 2018)
61	Baicalein  (Pubchem CID: 5281605)	NM; (C)	13.33 μmol/L	(Zuo et al., 2018)
62	Rosmarinic acid  (Pubchem CID: 5281792)	NM; (C)	6.67 μmol/L	(Zuo et al., 2018)
63	Dihydromyricetin 	NM; (C)	3.33 μmol/L	(Zuo et al., 2018)

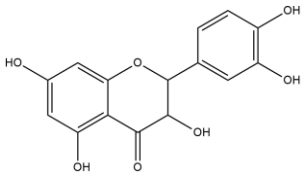
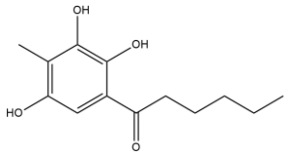
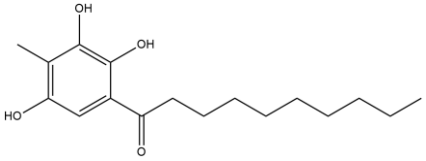
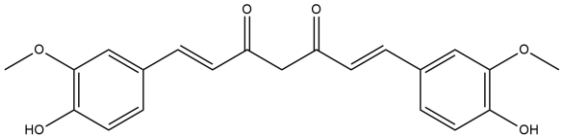
	(Pubchem CID: 161557)			
64	Kuwanon J  (Pubchem CID: 10394786)	Morus nigra; EtOH Extract (NM)	0.17 μM	(Hu et al., 2018)
65	Sanggenon O  (Pubchem CID: 15479637)	Morus nigra; EtOH Extract (NM)	1.15 μM	(Hu et al., 2018)
66	Broussoflavonol J (SNA) (Pubchem CID: NA)	Broussonetia papyrifera; EtOH (NM)	9.29 ± 0.28 μM	(Tian et al., 2019a)
67	Broussoflavonol H (SNA) (Pubchem CID: NA)	Broussonetia papyrifera; EtOH (NM)	13.69 ± 3.17 μM	(Tian et al., 2019a)
68	Broussoflavonol I (SNA) (Pubchem CID: NA)	Broussonetia papyrifera; EtOH (NM)	29.56 ± 4.22 μM	(Tian et al., 2019a)
69	Broussoflavonol K (SNA)	Broussonetia papyrifera;	17.56 ± 2.83 μM	(Tian et al., 2019a)

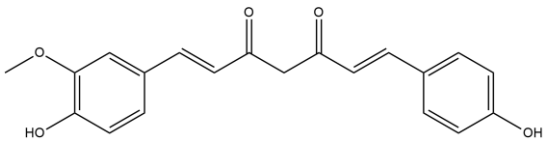
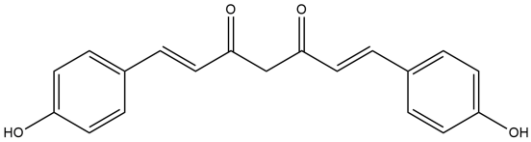
	(Pubchem CID: NA)	EtOH (NM)		
70	Glycyrrhiza flavonol A  (Pubchem CID: 5317765)	Broussonetia papyrifera; EtOH (NM)	20.67 ± 2.90 μM	(Tian et al., 2019a)
71	Papyriflavonol A  (Pubchem CID: 10343070)	Broussonetia papyrifera; EtOH (NM)	29.56 ± 3.64 μM	(Tian et al., 2019a)
72	Broussoflavonol F  (Pubchem CID: 9866908)	Broussonetia papyrifera; EtOH (NM)	29.65 ± 3.86 μM	(Tian et al., 2019a)
73	broussoflavonol B  (Pubchem CID: 480828)	Broussonetia papyrifera; EtOH (NM)	31.74 ± 1.96 μM	(Tian et al., 2019a)
74	Isolicofavonol  (Pubchem CID: 5318585)	Broussonetia papyrifera; EtOH (NM)	24.71 ± 3.59 μM	(Tian et al., 2019a)
75	7,8-dihydroxy-6-(3-methylbut-2-en-1-	Broussonetia	＞50 μM	(Tian et al.,

	yl)-2H-chromen-2-one (SNA) (Pubchem CID: NA)	papyrifera; EtOH (NM)		2019a)
76	Pterocarpan  (Pubchem CID: 6451349)	Dalbergia parviflora; (NM)	16.7 ± 5.0 μM	(Promden et al., 2018)
77	Khrinone B  (Pubchem CID: 44613667)	Dalbergia parviflora; (NM)	54.0 ± 6.0 μM	(Promden et al., 2018)
78	Cajanin  (Pubchem CID: 5281706)	Dalbergia parviflora; (NM)	67.9 ± 6.2 μM	(Promden et al., 2018)
79	5,5-dimethoxylariciresinol-4-O-βD-glucopyranoside (SNA) (Pubchem CID: NA)	Opilia Amentacea; EtOH (NM)	42.1 μM	(Magid et al., 2017)
80	Eleutheroside E1  (Pubchem CID: 443024)	Opilia Amentacea; EtOH (NM)	28 μM	(Magid et al., 2017)
81	Isosilybin A	Silybum	2.1 ± 0.2 μM	(Kim et al.,

	 (Pubchem CID: 11059920)	marianum; MeOH (M)		2019)
82	Isosilybin B  (Pubchem CID: 10885340)	Silybum marianum; MeOH (M)	4.9 ± 0.5 μM	(Kim et al., 2019)
83	Silydianin  (Pubchem CID: 11982272)	Silybum marianum; MeOH (M)	2.6 ± 0.1 μM	(Kim et al., 2019)
84	2,3-dihydrosilychristin  (Pubchem CID: 121232948)	Silybum marianum; MeOH (M)	7.6 ± 0.3 μM	(Kim et al., 2019)
85	Silychristin A	Silybum marianum; MeOH (M)	3.2 ± 0.3 μM	(Kim et al., 2019)

	 (Pubchem CID: 441764)			
86	Silychristin B  (Pubchem CID: 12442785)	Silybum marianum; MeOH (M)	4.5 ± 0.4 μM	(Kim et al., 2019)
87	Silybin  (Pubchem CID: 31553)	Silybum marianum; MeOH (M)	1.7 ± 0.07 μM	(Kim et al., 2019)
88	3'-O-methyltaxifolin  (Pubchem CID: 26194552)	Silybum marianum; MeOH (C)	51.2 ± 1.2 μM	(Kim et al., 2019)
89	Dihydrokaempferol  (Pubchem CID: 122850)	Silybum marianum; MeOH (C)	73.6 ± 1.8 μM	(Kim et al., 2019)
90	Taxifolin	Silybum marianum; MeOH (C)	23.0 ± 0.9 μM	(Kim et al., 2019)

	 (Pubchem CID: 439533)			
91	1-(2,3,5-trihydroxy-4-methylphenyl)hexane-1-one  (Pubchem CID: 132275589)	Syzygium polyanthum; MeOH (NM)	125.34 μM	(Setyawati et al., 2018)
92	1-(2,3,5-trihydroxy methylphenyl)octane1-one (SNA) (Pubchem CID: NA)	Syzygium polyanthum; MeOH (NM)	480.51 μM	(Setyawati et al., 2018)
93	(4E)-1-(2,3,5-trihydroxy-4-methylphenyl)decan-1-one (SNA) (Pubchem CID: NA)	Syzygium polyanthum; MeOH (NM)	83.98 μM	(Setyawati et al., 2018)
94	1-(2,3,5-trihydroxy-4-methylphenyl)decan-1-one  (Pubchem CID: 129862762)	Syzygium polyanthum; MeOH (NM)	> 1000 μM	(Setyawati et al., 2018)
95	Seguinoside A p-coumarate (SNA) (Pubchem CID: NA)	Breynia officinalis; MeOH (NM)	16.9 ± 2.3 μM	(Sasaki et al., 2018)
96	Curcumin  (Pubchem CID: 969516)	Curcuma longa; (M)	326.5 μM	(Athipornchai et al., 2021)
97	Demethoxycurcumin	Curcuma	470.0 μM	(Athipornchai

	 (Pubchem CID: 5469424)	longa; (M)		et al., 2021)
98	Bisdemethoxycurcumin  (Pubchem CID: 5315472)	Curcuma longa; (M)	46.5 μM	(Athipornchai et al., 2021)

NA= Not Available SNA= Structure Not Available

NC= Non-competitive; C= Competitive; M= Mixed; NM= Not Mentioned; NT= Not Tested

Table 3. List of reported medicinal plant's showing Tyrosinase inhibitory activity with their IC_{50} values.

Sl. no	Medicinal Plant Name/ Part Used	Extract/Mode of Inhibition	IC_{50} value	References
1	Red koji extracts	Water; (C)	5.57mg/mL	(Wu et al., 2003)
2	*Pueraria lobata* - Stem extract	MeOH, $CHCl_3$, EtOAc, and BuOH; (NM)	52.6%, 63.9%, 36.6%, and 7.3%	(Tan et al., 2016)
3	*Dalbergia parviflora* – Heartwood extract	NM	2.6 ± 0.4 μg/mL	(Promden et al., 2018)
4	*Ficus virens* - Leaves, Fruit, and Stem bark extracts	Acetone; (M)	131.67, 99.89, & 106.22; 128.42, 43.07, & 74.27 μg/ml	(Chen et al., 2014)
5	*Vigna angularis* – Seed extract	Acetone; (M)	130.0 (MP) &	(Chai et al.,

			35.1 (DP) µg/mL	2019)
6	*Leucaena leucocephala* – Leaf and fruit extract	Acetone: water (70:30); (M)	52.3 (MP) & 16.1 (DP) µg/mL	(Chen et al., 2018)
7	*Vigna radiata* – Seed extract	Acetone: water (70:30); (M)	80 (MP) & 20 (DP) µg/mL	(Chai et al., 2018)
8	*Prunus cerasifera* – Leaf extract	Acetone: water (70:30); (M)	738.37 (MP) & 137.69 (DP) µg/mL	(Song et al., 2018)
9	*Annona squamosa* – Fruit (pericarp) extract	Acetone: water (70:30); (C)	46.5 (MP) & 37.3 (DP) µg/mL	(Chai et al., 2017b)
10	*Clausena lansium* – Fruit (pericarp) extract	Acetone: water (70:30); (MC)	23.6 (MP) & 7.0 (DP) µg/mL	(Chai et al., 2017c)
11	*Ficus altissima* – Leaf extract	Acetone: water (70:30); (M)	256.7 (MP) & 41.3 (DP) µg/mL	(Deng et al., 2016)
12	*Rhododendron pulchrum* - Leaf extract	Acetone: water (70:30); (MC)	200 (MP) & 200 (DP) µg/mL	(Chai et al., 2015a)
13	*Persea americana* – Fruit extract	Acetone: water (70:30); (C)	40 (MP) & 19.5 (DP) µg/mL	(Chai et al., 2015b)
14	*Syzygium polyanthum* – Leaf extract	MeOH; (NM)	35.45 µg/mL	(Setyawati et al., 2018)
15	*Harpephyllum caffrum* – Leaf & Bark extract	EtOH; (NM)	51 ± 0.002 & 40 ± 0.035 µg/mL	(Mapunya et al., 2012)

16	*Hyaenanche globose* – Aerial part extract	MeOH; (NM)	27.1 ± 042 µg/mL	(Momtaz et al., 2008)
17	*Pituranthos scoparius* – Aerial part extract	Aqueous ethanol (50 %); (NM)	125.01 ± 0.72 µg/mL	(Jdey et al., 2017)
18	*Cleome arabica* - Aerial part extract	Aqueous ethanol (50 %); (NM)	124.4 ± 0.69 µg/mL	(Jdey et al., 2017)
19	*Haloxylon articulatum* - Shoot extract	Aqueous ethanol (50 %); (NM)	160 µg/mL	(Jdey et al., 2017)
20	*Rorippa nasturtium-aquaticum* – Leaf extract	Aqueous ethanol (70 %); (NM)	1.513 & 22.24 µg/mL	(Thibane et al., 2019a; Thibane et al., 2019b)
21	*Cassipourea flanaganii* – Bark extract	Aqueous ethanol (70 %); (NM)	22.24 ± 1.32 & 1.425 µg/mL	(Thibane et al., 2019a; Thibane et al., 2019b)
22	*Ormocarpum trichocarpum* – Leaf and stem extract	EtOH; (C)	2.95 ± 1.76 µg/mL	(Stapelberg et al., 2019)
23	*Vachellia karroo* – Root extract	EtOH; (C)	6.84 µg/mL	(Stapelberg et al., 2019)
24	*Acacia nilotica* – Pod extract	MeOH extract (NM)	8.61 ± 0.94 & 12.97 ± 1.07 µg/mL	(Muddathir et al., 2017; Lall et al., 2019)
25	*Plectranthus ecklonii* – Aerial part extract	Ethyl acetate & chloroform; (NM)	61.73 ± 2.69 & 21.58 µg/mL	(Nyila, 2011)
26	*Greyia flanaganii* – Leaf extract	(NM)	17.86 µg/mL	(Mapunya

				and Lall, 2011)
27	*Greyia radlkoferi* - Leaf extract	EtOH; (NM)	17.96 µg/mL	(Lall et al., 2016)
28	*Myrsine Africana* – Shoot extract	MeOH; (NM)	22.51 ± 0.42 & 27.4 µg/mL	(Kishore et al., 2018)
29	*Sesamum angolense* – Leaf extract	MeOH; (C)	24 µg/mL	(Kamagaju et al., 2013)
30	*Dolichopentas longiflora* – Leaf extract	MeOH; (C)	26 ± 2 µg/mL	(Kamagaju et al., 2013)

C= Competitive; M= Mixed; MC= Mixed competitive; NM= Not Mentioned; MP- Monophenolase Activity; DP- Diphenolase Activity.

Natural Tyrosinase Enzyme Inhibitors: A path from melanin to melanoma and its reported pharmacological activities

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Abstract

The skin containing melanin pigment acts as a protective barrier and counteracts the UVR and other environmental stressors to maintain or restore disrupted cutaneous homeostasis. The production of melanin pigment is dependent on tyrosine levels. L-tyrosine and L-dihydroxyphenylalanine (L-DOPA) can serve both as a substrates and intermediates of melanin synthetic pathway and as inducers and positive regulators of melanogenesis. The biosynthesis of melanin is stimulated upon exposure to UVR, which can also stimulate local production of hormonal factors, which can stimulate melanoma development by altering the chemical properties of eu- and pheomelanin. The process of melanogenesis can be altered by several pathways. One involves activation of POMC, with the production of POMC peptides including MSH and ACTH, which increase intracellular cAMP levels, which activates the MITF, and helps to stimulate tyrosinase (TYR) expression and activity. Defects in OCA1 to 4 affects melanogenic activity via posttranslational modifications resulting in proteasomal degradation and reducing pigmentation. Further, altering, the MITF factor, helps to regulate the expression of MRGE in melanoma, and helps to increase the TYR glycosylation in ER. CRH stimulates POMC peptides that regulate melanogenesis and also by itself can stimulate melanogenesis. The POMC, P53, ACTH, MSH, MC1R, MITF, and 6-BH4 are found to be important regulators for pigmentation. Melanogenesis can affect melanoma behaviour and inhibit immune responses. Therefore, we reviewed natural products that would alter melanin production. Our special focus was on targeting melanin synthesis and TYR enzyme activity to inhibit melanogenesis as an adjuvant therapy of melanotic melanoma. Furthermore, this review also outlines the current updated pharmacological studies targeting the TYR enzyme from natural sources and its consequential effects on melanin production.

Keywords: Melanoma, Tyrosinase inhibitors, Melanin, Melanogenesis, Skin Pigmentation, and Skin cancer.

Abbreviations

Cutaneous melanoma, CM

Acral lentiginous melanoma, ALM

Ultraviolet, UV

Tyrosinase, TYR

Hypoxia-inducible factor 1-alpha, HIF-1α

Proopiomelanocortin, POMC

Melanin stimulating hormone, MSH

Melanocortin 1 receptor - MC1R

Microphthalmia-associated transcription factor, MITF

Nitric Oxide synthase, NOS

Nicotinamide adenine dinucleotide phosphate, NADPH

Tetrahydro-biopterin, 6-BH4

Cyclin-dependent kinase inhibitor 2A, CDKN2A or p16

Cyclin-dependent kinase 4, CDK4Familial atypical multiple mole-melanoma, FAMMM

Nucleotide excision repair, NER

Neurofibromatosis type 1, NF1

Phosphatase and tensin homolog, PTEN

Tumor Protein 53, TP53

Telomerase Reverse Transcriptase, TERT

AT-rich interactive domain-containing protein 2, ARID2

Mitogen-Activated Protein Kinase, MAPK

L-3,4-dihydroxyphenylalanine, L-DOPA

5,6-dihydroxyindole, DHI

5,6-dihydroxyindole-2-carboxylic acid, DHICA

Tyrosinase-related protein 1, TYRP1

Tyrosinase-related protein 2, TYRP2

Epidermal growth factor, EGF

Endoplasmic reticulum, ER

Menkes copper transporter, MNK

Cysteine, Cys

Copper, Cu

Oculocutaneous albinism type 1, OCA1

Oculocutaneous albinism type 2, OCA2

Oculocutaneous albinism type 3, OCA3

Oculocutaneous albinism type 4, OCA4

Trans-Golgi Network, TGN

ER-associated protein degradation, ERAD

Adrenocorticotropic hormone, ACTH

Corticotropin releasing hormone, CRH

Hypothalamic pituitary adrenal, HPA

Vacuolar ATPase, v-ATPase

Melanogenesis-related gene expression,

MRGE

1.1. Introduction

Melanoma arises through malignant transformation of melanocytes, melanin producing cells, as shown in **Figure 1**. Due to its ability to metastasize to other parts of the body, it is one of the most aggressive types of all skin cancers (DeVita and Lawrence, 2008; Mitchell et al., 2020). It accounts for 1% of all skin tumors but has a mortality rate of up to 60% (Khazaei et al., 2019). Melanoma is of significant concern for the Caucasian population, and its incidence is increasing globally. In 2018, there were 2,87,723 cases and 60,712 deaths reported due to melanoma by WHO, which accounted for 0.6 % of deaths due to melanoma alone (WHO, 2019). The prevalence of cutaneous melanoma (CM) varies significantly among different populations, and these variations are due to distinct skin phenotypes and different levels of sun exposure. The acral lentiginous melanoma (ALM) is the most commonly seen variant with the Asian population (Phan et al., 2006). ALM is a malignant tumor or histological subtype of CM that occurs in the glabrous skin of the palms, soles, and nails, and it carries one of the worst prognoses among other subtypes. Furthermore, in contrast to other solid tumors, young to middle-aged individuals are more often affected by melanoma, and the incidence rate is augmented linearly between the age of 25 and 50 (Bressac-de-Paillerets et al., 2002; Leonardi et al., 2018). In addition, climate changes, increased amount of arsenic in water, ozone depletion, and numerous other factors like naevi have demonstrated to show direct associations with melanoma (Fabbrocini et al., 2010).

Melanin protects from ultraviolet radiation (UVR) induced malignant transformation of melanocytes. However, its role in melanoma progression is complex. This is recently discussed by Slominski and co-workers (Slominski et al., 2022), stated that melanin protects against the development of skin cancers including cutaneous melanoma, and its presence is necessary for the transformation of melanocytes (Slominski et al., 2022). Melanocytes produce

melanin, which contains both eumelanin, and pheomelanin, through a series of oxidoreduction processes. The enzyme tyrosinase (TYR) catalyses the hydroxylation of L-tyrosine to L-DOPA, which is further oxidized to DOPAquinone, a starting process of melanogenesis (Hearing and Tsukamoto, 1991; Pawelek et al., 1992; Pawelek, 1993; Chung et al., 2018). The melanin is then deposited in the melanosomes, which are transported to keratinocytes, finally defines the skin and hair colour (Wasmeier et al., 2008; Garibyan and Fisher, 2010; Kim et al., 2018). The coordinated levels of eumelanin and pheomelanin regulate the skin physiological adaptation upon exposure to UVR. This shows a complex role of melanogenesis, defined by the chemical properties of melanin and the nature generating pathways such as eu- and pheomelanogenesis, which may affect the process of melanoma development. Thus, eumelanin acts as an effective antioxidant, and acts as a sunscreen and is believed to provide radio and photoprotection, whereas pheomelanin, generates mutagenic environment after exposure to UVR. Intermediates of melanogenesis are highly reactive and have cytotoxic, genotoxic, and mutagenic activities. Melanogenesis can stimulate glycolysis and hypoxia-inducible factor 1-alpha (HIF-1α) (Slominski et al., 2014), which can lead to the progression of melanoma and can affect resistance to immunotherapy (Slominski et al., 2022). Thus, dysregulated levels of eu- and pheomelanin can lead to various skin pathological conditions such as skin diseases and pigmentary disorders (Garibyan and Fisher, 2010). Although the primary role of melanin is to defend the skin against UVR and injury (Brenner and Hearing, 2008; Schallreuter et al., 2008), it can affect radiotherapy (Brozyna et al., 2016) and overall disease-free survival in patients with stage III and IV melanoma (Brozyna et al., 2013). As TYR plays a pivotal role in melanogenesis, it is considered to be a putative therapeutic target for combating melanoma (D'Mello et al., 2016).

Given the increasing incidence of melanoma, considerable attention has focused on to develop newer and improved strategies such as use of pro-drugs for treating the disease. The

pro-drugs are activated by TYR targeting melanoma, and could be an interesting *in-situ* tool for the treatment of melanoma, but it tends to form toxic metabolites and thus require alternative approach therapy (Rooseboom et al., 2004; Gasowska-Bajger and Wojtasek, 2008; Jawaid et al., 2009). Natural products including phytochemicals are reported to possess a wide number biological activities mainly flavonoids, alkaloids, glycosides, terpenoids (Hasanpourghadi et al., 2017), and recently have gained more attention towards chemotherapy, and also shows promising activity against various tumors (Nobili et al., 2009; Turek et al., 2016; Shanmugam et al., 2016). Further, based on these collated reports natural products could be a potential weapon in combating cancer (Naviglio and Della Ragione, 2013; Shanmugam et al., 2016). Therefore, this review discusses in detail on the TYR regulation, and its role in melanogenesis, with potential targeting TYR in treatment of melanoma.

1.2. Role of UVR in melanoma

The UVR from the sun is considered to be the primary ecological reason in the development of melanoma (Gilchrest et al., 1999; Leonardi et al., 2018). Melanoma develops when melanocytes proliferate rapidly, occurs due to UVR -induced DNA mutations, which account for about 65% of melanoma occurrences in skin (Armstrong, and Kricker, 1993). The skin, is a self-regulating protective barrier, empowered with sensory capabilities to counteract the environmental stress and helps to maintain and restore the disrupted cutaneous homeostasis (Slominski and Wortsman, 2000; Slominski et al., 2012; Slominski et al., 2022). These functions are completely coordinated by cutaneous neuro-endocrine system that communicates with the central nervous, endocrine, and immune systems in a bidirectional way, and plays a potential role in controlling body homeostasis (Slominski and Wortsman, 2000; Slominski et al., 2022). However, the energy obtained from UVR is absorbed by skin, which triggers the mechanisms that defend skin integrity, and also regulates the body homeostasis (Slominski et al., 2018). Therefore, the UVR acts by touching the brain and central neuroendocrine system

in order to reset the body homeostasis (Skobowiat et al., 2011, Slominski et al., 2018). The epidermal melanin has an important physiological implication in humans, were higher content of melanin helps to protect against UVR-induced skin damage via optical and chemical properties (Ahene et al., 1995). The pigment amounts were found higher in regions of lower latitude and higher UVR levels were observed in skin. This may be directly associated with humans in early hominids having dark and dense coloured hair. Post et al., reported on the closely related primate i.e., chimpanzees, and showed to exhibit white or light colour pigment in the epidermal layer (Post et al., 1975). Interestingly, chimpanzees have active melanocytes that are present in the epidermis of those areas, which are directly exposed to UVR (Montagna and Machida, 1966).

Therefore, in order to maintain thermal balance in human epidermis, which leads to an progressive increase in demands for heat dissipation, and further resulting from enhanced blood flow to the brain (Pagel and Bodmer, 2003). Thus, an increased epidermal melanization occurs due to high exposure to UVR in humans, which potentially could lead to adverse effects, such as sunburns and causes damage to the sweat glands resulting in the suppression of sweating and abnormal thermoregulation (Pandolf et al., 1992), and can induce carcinogenesis, and inactivation of nutrient by photolysis (Branda and Eaton, 1978; Slominski et al., 2004).

The epidermal melanocytes, are pigment producing and secretary cells of the neural crest that communicates with multiple targets. Slominski et al., reported on the normal epidermal melanocytes, which are sensory and regulatory cells operating in the context of regulatory network that helps to maintain the epidermal homeostasis in humans (Slominski et al., 1993a; Slominski, 2009a). Thus, the functions of altered melanocyte, plays a major role in other diseases like skin disease, and racial pigmentation, which may affect the cutaneous functions (Slominski et al., 1993; Barsh, 1996).

The activation of the proopiomelanocortin (POMC) expression, production and release of POMC derived peptides including ACTH, melanocyte stimulating hormone (MSH) and β-endorphin from keratinocytes, helps to stimulate the melanocytes or fibroblasts causing melanocyte differentiation (Slominski et al., 2000; Slominski et al., 2004). These melanocytes respond to the MSH via polymorphic receptor melanocortin 1 receptor (MC1R). Thus, activation of this receptor causes increase in the cAMP levels and further activates the transcription of microphthalmia-associated transcription factor (MITF) (Garibyan and Fisher, 2010). This signalling mechanism results in the initiation of melanin synthesis through stimulation of TYR, and leads to the protection of keratinocytes from DNA damage. In the keratinocytes, UVR activates nitric oxide synthase (NOS) type 1, leading to increased nitric oxide and TYR levels, causing subsequent acceleration of melanogenesis. The activity of the NOS cofactors, including calcium, nicotinamide adenine dinucleotide phosphate (NADPH), and tetrahydro-biopterin (6-BH4), were also elevated upon exposure to UVR. Among these cofactors, activation of 6-BH4 leads to the activation of NOS type 1, but still the mechanism involved in it is unclear (Roméro-Graillet et al., 1997). Apart from that, 6-BH4 is also involved in modulating the TYR enzyme activity. The 6-BH4 is a vital cofactor and an electron donor in the conversion of L-phenylalanine to L-tyrosine occurs via hydroxylation. It acts as a rate-limiting factor in controlling the production of L-tyrosine (Schallreuter et al., 1994). Additionally, the redox switch between 6-BH4 and 6-biopterin controls TYR activity and regulates melanogenesis, but photo-oxidation of 6-BH4 occurs upon exposure to UVR and could lead to elevated TYR activity (Wood et al., 1995). Thus, exposure to UVR alters the regulation of NOS type 1 activity, tyrosine production, and TYR activity. Therefore, this showed to elevate the expression of UVR-induced 6-BH4 levels and increased photo-oxidation, which may also lead to cancer conditions (Wood et al., 1995). In addition, melanoma develops as a result of interactions between genetic and environmental factors. Excessive exposure to

UVR, can cause increase in the melanoma penetrance in melanoma-prone families. For instance, in a study on melanoma-prone families, patients' with "9p-linked" gene, were altered due to excessive exposure to UVR regardless of their skin type showed increased chance of developing melanoma (Cannon-Albright et al., 1994).

Of note, about 5-12% of melanoma with the distinct mutation has been reported to be of hereditary origin (Rebecca et al., 2012). These mutations in cyclin-dependent kinase inhibitor 2A (*CDKN2A* or p16) and cyclin-dependent kinase 4 (CDK4) are most frequently identified in the families prone to familial atypical multiple mole-melanoma (FAMMM) (Gruis et al., 1995; Zuo et al., 1996; Soura et al., 2016). Further, changes in the *CDKN2A* gene mutation showed to possess about 40% of familial melanomas, which resulted in defective tumor suppressor proteins p14 (*p14ARF*) and p16 (*p16INK4A*), and further stabilizes p53 gene by regulating the G1 checkpoint (Rebecca et al., 2012; Shain and Bastian, 2016). Interaction of p16 with CDK4 results in cell cycle arrest, whereas mutations in p16 (p16INK4A), helps to inhibit the binding of p16 to CDK4, and thereby interrupts the cell cycle arrest (Mehnert and Kluger, 2012). Mutation in the nucleotide excision repair (NER) pathway, which is another group of germline mutation, identified to augment the risk of developing melanoma (Davis et al., 2019). These mutations are more pathogenic, and are less common. Further, intensive exposure to UVR can causes DNA lesions, which are removed by NER mechanism. Therefore, genetic mutations in NER pathways results in increased UVR-induced unrepaired DNA damage.

Melanomas are also associated with recurrent somatic mutations. Most frequently, the key mutations occur in the signalling pathways are (a) *BRAF*, *NRAS*, and neurofibromatosis type 1 (NF1), which plays an important role in regulating the proliferation of cells (Scolyer et al., 2011), (b) Phosphatase and tensin homolog (PTEN) and *KIT* that coordinates the growth and metabolism (Read et al., 2016), (c) Tumor Protein 53 (TP53) which regulates resistance to

apoptosis (Scolyer et al., 2011), (d) Telomerase reverse transcriptase (TERT) – regulates replicative lifespan (Horn et al., 2013; Read et al., 2016), (e) AT-rich interactive domain-containing protein 2 (ARID2) – responsible for cell identity (Scolyer et al., 2011) and (f) *CDKN2A* – responsible for cell cycle arrest (Scolyer et al., 2011; Read et al., 2016). Although melanomas arise from somatic mutations, most of them could develop due to acquired mutations. For instance, mitogen-activated protein kinase (MAPK) is the most commonly mutated pathway, and these mutational events were prevalent in 70% of melanoma patients (Scolyer et al., 2011). Similarly, about 80% of them contain *BRAF* mutations, were V600E is the most common mutation of BRAF that is over >85%, and activates the downstream MAPK oncogenic pathway. Together, it is apparent that MAPK cascades have potential implications in UVR-induced carcinogenesis. Yet, the mechanism by which MAPK cascades orchestrate UVR exposure-driven melanoma remains elusive (Bode and Dong, 2003).

1.3. Role of melanin and melanogenesis in regulating cellular metabolism

The movement of mature melanosomes from melanocytes into keratinocytes via lysosomal compartment, occurs in the upper epidermal layer forming melanin granules. Furthermore, precise mechanism of melanin breakdown or degradation remains to be investigated. The melanin is highly resistant to enzymatic lysis, and reports showed that phagosomal NADPH oxidase enzyme degrades the melanin via oxidation (Borovansky and Elleder, 2003). Unlike those in overlying epidermis, the melanin granules remain intact in the hair shaft and this occurs mainly in the black hair shaft containing eumelanogenic melanosomes, which are often seen in East-Asian individuals containing high-density pigment granules.

Melanin can reduce the effect of UV penetration to blood in humans. The highest UV absorption for oxyhemoglobin can be identified at a wavelength of 545 nm, which causes strong erythema reaction with subsequent pigmentary response with individuals having light

skin. Therefore, when exposed to UVR, melanin undergoes photosensitization producing superoxide radicals, causing harmful injury to cells. This process could possibly lead to a condition called cell neoplasia, causing low proliferation rate in normal skin cells (Furuya et al., 2002), and consisting of a linkage between melanin production and UVR-induced DNA damage, i.e., responsible for maintaining the skin homeostasis and tanning (Gilchrest and Eller, 1999). Therefore, understanding pathophysiology of pigmentation, occurs mainly due to the exposure of melanin to various toxic metabolites, resulting in higher melanin granules and deposition, which could be possible reason of pigmentation (Lindquist, 1973; Slominski et al., 2004).

Melanin plays an imperative role in preventing melanoma formation (Gilchrest et al., 1999), as it protects the skin from UVR-induced DNA damage and genetic changes. However, repetitive exposure decreases its protective function, resulting in cancer progression (Armstrong and Kricker, 1993). TYR plays a crucial role in the synthesis of melanin as it is the rate-limiting enzyme of the pathway, possessing both monophenolase and diphenolase activities, which enable oxidation of tyrosine to L-DOPA, and is said to be the first and most critical step in the synthesis of melanin. Melanin synthesis involves hydroxylation of L-tyrosine to L-DOPA and subsequently its oxidation to DOPA-quinone. Next, DOPA-quinone cyclizes to form DOPA-chrome, leading to the production of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA). TYR catalyses the oxidative polymerization of DHI. TYR- related protein 1 catalyses the oxidation of DHICA and leads to the formation of melanochrome and converted to an insoluble eumelanin pigment (Raper, 1928; Korner and Pawelek, 1982; Wang and Hebert, 2006). Also, in the presence of cysteine and glutathione, DOPA-quinone is converted to 5-S-cysteinyl-DOPA and cystathionyl-DOPA, respectively then later converted to pheomelanin (Pillaiyar et al., 2015).

1.4. Tyrosinase enzyme and its intrinsic roles

The key regulatory enzyme of melanogenesis, is TYR a product of c-locus that maps to the chromosome 11q14–21 in humans (Barton et al., 1988) and chromosome 7 in mice, respectively, consisting of five exons and four introns (Kwon, 1993; Thody, 1995; Nordlund et al., 1998). The TYR mRNA generates several alternatively spliced products while posttranscriptional processing occurs (Shibahara et al., 1988; Porter and Mintz, 1991; Kelsall et al., 1997; Le Fur et al., 1997), of which some are translated to protein products expressing TYR activity (Muller et al., 1988; Ruppert et al., 1988). It is proposed that the obtained products from TYR mRNA could be best served as regulatory protein (Slominski and Paus; 1990; Slominski and Paus; 1994), and acts as a receptor for L-tyrosine and L-DOPA (Slominski and Paus, 1994). Also, it is noted that non-functional TYR proteins express non-melanocytic cells (Haninec and Vachtenheim, 1988; Tief et al., 1998). There is evidence that L-tyrosine and L-DOPA, besides serving as a substrates and intermediates for melanogenesis, and also act as a bioregulatory agents, and inducers, which shows positive regulators of melanogenesis, leading to regulation of the cellular functions (Slominski and Paus, 1990; Slominski et al., 2012).

TYR catalyses three distinct reactions in the melanogenic pathway; i.e., hydroxylation of L-tyrosine, dehydrogenation of L-DOPA, and dehydrogenation of DHI; where L-DOPA serves as cofactor in the first and third reactions (Lerner and Fitzpatrick, 1950; Korner and Pawelek, 1982; Pawelek and Korner, 1982; Hearing and Tsukamoto, 1991). Both hydroxylation of tyrosine and dehydrogenation of L-DOPA requires single step, where the substrate binding site are the same, and the reaction involves exchange of electrons with copper atoms generating orthoquinone and water as final products (Nordlund et al., 1998; Riley, 2000; Land et al., 2003a; Land et al., 2003b; Slominski et al., 2004). Slominski et al., reported on the role of L-tyrosine, L-DOPA, and TYR as a positive-regulators of melanogenesis in Bomirski Ab amelanotic hamster melanoma cells. Their findings showed that synthesis of subcellular

level of melanogenesis is initiated by L-tyrosine and is further regulated by TYR and L-DOPA, which serves as a second messenger to tyrosine hydroxylase activity (Slominski et al., 1989; Slominski and Paus, 1994).

The TYR protein structure is different among highly conserved species and shows high homology with other tyrosinase-related proteins, such as tyrosinase-related protein 1 (TYRP1) and 2 (TYRP2). In this protein the TYR comprises of NH_2 terminal domain signalling peptide responsible for intracellular trafficking and processing, the epidermal growth factor (EGF)-like/cysteine-rich domain, has two histidine regions, and copper (Cu) binding site with a cysteine region acting as an important catalytic domain, and COOH-terminal with hydrophobic transmembrane segment and a cytoplasmic tail (Kwon et al., 1987; Shibahara et al., 1988; Kwon, 1993; Nordlund et al., 1998). These transmembrane and cytoplasmic domains are important for targeting the enzyme to melanosome (Jimbow et al., 2000a; Jimbow et al., 2000b; Selaturi, 2000), while the NH_2 terminal with cysteine region may serve as a protein binding/regulatory domain unrelated to enzymatic function. Later, the newly synthesized TYR has about 55–58 kDa molecular mass with an isoelectric point of 4.2. These requires proper folding of TYR protein and is crucial for further transport to Golgi apparatus in the endoplasmic reticulum (ER). Therefore, the proteolytic cleavage of the transmembrane portion of newly synthesized enzyme generates two soluble forms: a 53-kDa unmodified protein, or a 65-kDa glycosylated TYR, which may be active in the melanosome or secreted into the extracellular environment. After glycosylation in the trans-Golgi complex, there is an increase in the size of TYR of about 65–75 kDa or even 80 kDa (Hearing and Tsukamoto, 1991; Sanchez-Ferrer et al., 1995; Del Marmol and Beermann, 1996a; Del Marmol et al., 1996; Jimbow et al., 2000). The higher molecular mass of TYR (Slominski A and Costantino, 1991; Slominski et al., 1991a; Slominski et al., 1991b; Sanchez-Ferrer et al., 1995; Del Marmol and Beermann, 1996a), may possess tight complexes with other melanogenic (Orlow et al., 1994), or high-

molecular-weight TYR proteins. When copper ions, are necessary for the enzymatic activity, they integrate into apo-TYR, which is still unclear. However, recent data suggests that the Menkes copper transporter (MNK) is required for copper loading of TYR enzyme necessary for its activation (Petris et al., 2000). The catalytic site of TYR is represented by two copper atoms ligated to six histidine residues.

TYR is a metalloenzyme with a highly conserved bi-copper active center (Ramsden and Riley, 2014); however, its structural properties are distinct in bacteria, plants, and mammals (Solano, 2014). In the mushrooms and vertebrates, the TYR catalyses the initial steps in forming the melanin pigment using tyrosine. In contrast, the plants use the composition of phenols as a substrate (Casanola-Martin et al., 2014). In mammals, it is expressed abundantly in melanocytes, but it is also present in the epithelial layer of the retina, iris, and ciliary parts of the eye (Saeki and Oikawa, 1980). TYR is classified under type-I membrane glycoproteins and consists of three conserved domains; N-terminal signal domain, solitary transmembrane α-helix, and C-terminal cytoplasmic domain. The N-terminal domain of TYR is responsible for the catalytic activity. It comprises of 17 cysteines (Cys) residues present as 3 clusters and 7 N-linked glycosylation sites present throughout the region. Among 17 Cys residues, 15 residues are freely available for the disulphide bonding, whereas one residue is removed by signal sequence locally and another residue is removed in the cytoplasmic tail. The solitary hydrophobic transmembrane domain consists of 26 amino acid sequences and it anchors the TYR into the melanosome membrane (Wang and Hebert, 2006). This cytoplasmic domain harbors a melanosome sorting signal that traffic the protein to the melanosomal membrane. The two Cu atoms in the active cite of the enzyme are harmonized with three histidine residues that anchor dioxygen binding to the peroxy configuration (Ramsden and Riley, 2014). This dioxygen bonds with Cu at the active site comprises of the amino acid sequence of His162,

184, and 193, which are referred to as CuA whereas, CuB includes His345, 349, and 371, respectively (Wang and Hebert, 2006).

The enzyme TYR possesses four oxidation states, met-, oxy-, deoxy-, and deact-TYR, which play an imperative role in melanin production (Ramsden and Riley, 2014). Oxy-TYR or oxygenated form entails two tetragonal Cu (II) atoms. Both of them are coordinated with strong dual equatorial and single weak axial N_{His} ligand, and two Cu atom centers that are linked by the peroxide, forming exogenous oxygen molecule. Likewise, met-TYR comprises of two tetragonal Cu (II) ions bridged by water or hydrophobic ligands. In this form, other than peroxide, there are few hydroxide ligands that are also attached exogenously to the Cu binding site. Deoxy-TYR comprises of twin Cu (I) ions, which synchronizes parallel to the met form, and lacks the hydroxide bridge in the ring structure. Therefore, the enzyme that is achieved after purification will comprise of both met and oxy forms in the ratio 85:15 (Chang, 2009). The met-TYR has a null role in catalysing the conversion of substrates i.e., catechol and phenols to ortho-quinones. Conversely, the deoxy-TYR oxidizes phenols and catechols in the monophenolase and diphenolase phases, respectively. The catechol oxidation in monophenolase phase by oxy-TYR leads to elimination of Cu atoms in the active site and irreversible formation of deoxy-TYR, which subsequently results in deactivation of the enzyme (Ramsden and Riley, 2014).

Defects in the TYR gene leads to a condition called as oculocutaneous albinism type 1 (OCA1) (Tomita et al., 1989; Takeda et al., 1990; Oetting and King, 1999). Due to the mutations in the Cu binding sites, the entire coding sequence of the gene is susceptible to mutations, which further leads to abnormalities in splicing (Oetting and King, 1999). Thus, the mutant TYR proteins are degraded by proteasomes enzyme, and allowing it to pass to the Golgi apparatus for glycosylation and further stops the transport to premelanosomes (Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Kushimoto et al., 2003; Toyofuku et al., 2001a;

Toyofuku et al., 2001b). Similarly, in oculocutaneous albinism type 3 (OCA3), the TYRP1 mutated is retained within ER and the process of normal TYR is terminated leading to proteasomal degradation and reduces pigmentation (Kushimoto et al., 2003; Toyofuku et al., 2001a; Toyofuku et al., 2001b). In case of oculocutaneous albinism type 2 (OCA2) and type 4 (OCA4), the TYR from trans-Golgi network (TGN) to melanosomes is disrupted (Chen et al., 2002; Toyofuku et al., 2002; Costin et al., 2003; Kushimoto et al., 2003). The experimental evidence suggested in various melanocytes, showed that ER is an essential step for TYR maturation, targeting melanosomes, and is an important step in the production of melanin pigment (Halaban, 2000; Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Halaban et al., 1997; Halaban et al., 2000). Thus, the defects underlying OCA1 via OCA4 showed melanogenic activity *in-vivo*, depends on the posttranslational pathways, of which the most important is the processing of TYR. In fact, the levels of TYR mRNA were found to be similar in both European and African individuals in cultured melanocytes (Iozumi et al., 1993), and also shows that TYR gene expression finds to be same among different human groups (Iwata et al., 1990; Fuller et al., 2001). On the other hand, dysregulation of the TYR melanogenic activity can be due to the lack of melanosomes, resulting in the accumulation of enzyme or blockade in the translocation from TGN to melanosomes (Bomirski et al., 1988; Slominski, 1988; Slominski et al., 1989), in the presence of intracellular TYR inhibitors or protein kinase-dependent phosphorylation (Wong and Pawelek, 1975; Korner and Pawelek, 1977; Kameyama et al., 1989; Park and Gilchrest, 1999; Slominski et al., 2004).

A plethora of studies suggests that UVR modulates the expression of TYR. The transcription factor MITF acts as a primary regulator of melanogenesis-related gene expression (MRGE) (Fuller et al., 1990), which subsequently regulates the mRNA levels of TYR and/or MITF in cultured melanoma (Lin et al., 2002; Ando et al., 2007). Therefore, increase in the glycosylation of TYR enzyme in the ER helps to inhibit the folding and maturation of melanin,

resulting in pigmentation (Imokawa, 1989). Thus, proteostasis of TYR is governed by the ER-associated protein degradation (ERAD) regulated by the ubiquitin-proteasome system, E3 ligases Doa10p and Hrd1p have been shown to ubiquitinate TYR, resulting in subsequent degradation (Hammond and Helenius, 1995; Bordallo et al., 1998). Further, transportation of TYR into melanosomes for melanogenesis is also dependent on ER. However, mutations in TYR result in TYR sequestration in ER and binds to ER-chaperones, calnexin, and calreticulin (Toyofuku et al., 2001a; Toyofuku et al., 2001b). This accumulated TYR is degraded through ERAD and thus inhibits its function (Smith et al., 2004). Therefore, ER plays a significant role in the regulation of TYR.

The pH critically modulates the TYR activity, and acidic pH is appropriate for its optimal tyrosine hydroxylase activity (Bhatnagar et al., 1993). The early melanosomes contain an acidic environment (Moellman et al., 1988; Raposo et al., 2001), where pH increases as the melanosomes mature, creating an optimal environment for TYR activity (Tucker and Goldstein, 2003). The incidence of melanoma is intensively increasing in Western countries (Fuller et al., 2001). In the Caucasian population, TYR activity for the synthesis of melanin is relatively less when compared with the darker skin-coloured population, even though the level of TYR mRNA and the enzyme are in abundance (Giebel et al., 1991), and the gene sequence were reported similar in both black as well as Caucasian population (Tachibana et al., 1996; Spritz et al., 1991). Also, the pH of melanosome and activity of TYR is controlled by the expression of vacuolar ATPase (v-ATPase) (Giebel et al., 1991; Ito and Wakamatsu, 2003). In the Caucasian population, higher expression of v-ATPase resulted in increased H^+ levels and produces an acidic environment in melanosomes. Conversely, in the African population, the expression of v-ATPase is low and hence requires to maintain acidic pH. Further, the melanin content in black skin is six times higher when compared to the white skin, particularly the levels of eumelanin (Kollias et al., 1991), whereas it was not so true in the case of pheomelanin

(Brenner and Hearing, 2008). In the black skin population, the melanosomes exist in single forms and works efficiently in the keratinocytes. In contrast, white skin forms clusters and translate as complex and work less efficiently (Pillaiyar et al., 2018). Together, these distinct mechanisms result in lower melanin production, which increases the risk and incidence of melanoma in Caucasians population. Therefore, it is apparent that the function of TYR is influenced by its substrates, cofactors, and cellular environmental factors. Also, the oxidation mechanism by the two Cu atoms present in the active site has been shown to influence the functions of TYR.

1.5. Role of POMC Expression in Skin

MSH was the first POMC peptide detected in the skin (Thody et al., 1983). Skin expresses the POMC gene and produces adrenocorticotropic hormone (ACTH) and □-endorphin (Slominski et al., 1993; Slominski and Mihm, 1996; Wintzen and Gilchrest, 1996; Luger et al., 1998; Slominski and Pawelek, 1998). The POMC gene transcription and translation in the mammalian skin was originally observed in C57BL/6 mice (Slominski et al., 1991; Slominski et al., 1992). Subsequently, POMC gene expression has been found in human skin, as well as in cutaneous cell culture systems (Slominski, 1991; Slominski, et al., 1991; Slominski, et al., 1992; Farooqui et al., 1993; Schauer et al., 1994; Chakraborty et al., 1995; Kippenberger et al., 1995; Slominski, et al., 1995; Slominski, et al., 1996; Chakraborty et al., 1996; Ermak and Slominski, 1997; Nagahama et al., 1998; Slominski, 1998; Slominski, et al., 1999; Slominski et al., 2000).

1.6. Role of corticotropin releasing hormone (CRH) in the epidermis

CRH has an important role in regulating the protective and homeostatic functions of the skin (Slominski et al., 2001; Slominski et al., 2013), where the synthesis of DNA occurs in the epidermal and dermal compartments, showing proliferation of cells in the keratinocytes (Slominski et al., 1999). Thus, stimulation of DNA synthesis is mainly achieved by adding

CRH to the telogen and anagen IV, in the keratinocytes (Slominski et al., 1999). However, in anagen II, the CRH has a opposite effect towards DNA synthesis, which showed to enhance the dermal DNA synthesis (Slominski et al., 1999). These reports suggest that CRH plays an important role in the proliferation of epidermal keratinocyte. Further, the exogenous CRH showed activity on the cellular levels targeting epidermal cycle dependent expression of CRH-related receptors. In order to determine the various contributing factors involving the exogenous CRH, which also includes endogenous production of CRH and CRH activated production of ACTH and MSH. It is well established that CRH at the systemic level regulates corticosterone (Nicolaides et al., 2015). Further, reports suggested that increased levels of CRH substantially increases the levels of corticosterone by stimulating the hypothalamic pituitary adrenal (HPA) axis (Wilson et al., 1998). Further, increased levels of glucocorticosteroid clearly showed to possess an anagen-inhibitory effect on CRH implants (Paus et al., 1994; Paus, 1996; Paus et al., 1999; Slominski et al., 2000).

1.7. Skin as a Target for POMC Peptides

The studies on the POMC knock-out mice model showed that surprisingly, these animals survived till the adulthood (Yawsen et al., 1999). This genotype led to the adrenal insufficiency, and leads to defects in melanin pigmentation (Yawsen et al., 1999). This is similar to patients with pituitary POMC gene mutations, which generates allelic forms with defective production of POMC protein (Hinney et al., 1998; Krude et al., 1998). Thus, the affected individuals possess red hair pigmentation, and shows adrenal insufficiency. There is a clinical report on excess POMC peptide syndromes that confirms skin as a potential target for POMC-derived peptides (Lerner and Mcguire, 1961; Moellmann et al., 1988; Lerner, 1993; Pawelek, et al., 1992; Pawelek, 1993; Slominski et al., 1993; Siegrist and Eberle, 1995; Wintzen and Gilchrest, 1996; Jordan and Jackson, 1998; Luger et al., 1998; Luger et al., 1999). For example, humans with pathologically increased levels of plasma ACTH levels in case of

Addison disease or excessive ACTH production by tumors in case of Nelson syndrome, showed hyperpigmentation and skin atrophy (Eberle, 1988), whereas administration of MSH or ACTH peptides showed in the stimulation of melanogenesis (Lerner, 1993; Lerner et al., 1961). Also, continuous administration of ACTH in humans causes acne, skin atrophy, hyperpigmentation, and hypertrichosis (Eberle, 1988). Thus, elevated levels of α-MSH in the serum concentrations are directly associated with skin pigmentation (Pears et al., 1992). Additional research performed on human and animal models, showed that immune, epidermal, adnexal, vascular, and dermal structures possessed additional targets for POMC peptides (Slominski et al., 2000). However, the effect of POMC on melanin pigmentation is conditional on functional agouti protein, since knocking of POMC gene in C57BL/6 mice, does not affect melanin production (Slominski et al., 2005).

1.8. Effects of CRH in malignant melanocytes

The CRH has a direct effect on melanocytes, where a study on hamster melanoma cell line, showed further insight into the mechanism of CRH action in the skin (Fazal et al., 1998; Slominski et al., 1999, 2000). Skin cells express corticotropin releasing hormone receptor 1 (CRH-R1) gene, where in case of melanoma, the CRH-R1 mRNA transcription was 2.5 kb long, being 0.2 kb shorter than that detected in normal skin cells (Slominski et al., 1999). Melanocytes and melanoma cells express G protein-coupled CRH-R1, which responds to CRH and acts mainly by activation of cAMP, IP3, and other mediated pathways and also acts by activating the Ca^{+} signalling to modify the melanocyte phenotype (Slominski et al., 2001; Slominski et al., 2006a; Slominski et al., 2006b). In normal and immortalized melanocytes, CRH inhibits the cell proliferation in serum-containing medium, inhibits early and late apoptosis in serum free media (Slominski et al., 2006a). Concerning melanoma cells, the effect was found to be heterogenous depending on the cells (Slominski et al., 2006a; Carlson et al., 2001). The variability in CRH action in the melanoma cells could be explained by co-

expression of alternatively spliced CRH-R1 isoforms on the same cells that helps to modify the action of the CRH-R1α isoform (Slominski et al., 2001; Slominski et al., 2006b). Of significance, antimelanoma effect for selective CRH-R1 agonists has already been observed in *in-vivo* experimental models of melanoma (Carlson et al., 2001). Accordingly, selective targeting of CRH-R1 has been proposed for the treatment of malignant tumors that also include melanoma (Patent No: WO0153777).

1.9. Pharmacological approaches modulating TYR activity

A wide number of compounds from medicinal plants have been reported to inhibit melanogenesis by modulating the glycosylation of TYR enzyme (Imokawa and Mishima, 1982; Imokawa, 1989; Mineko et al., 1992; Petrescu et al., 1997; Pillaiyar et al., 2017). Selective approaches targeting TYR expression, degradation, and maturation are emerging as promising leads, including inhibition of TYR enzyme mRNA transcription (**Table 1**), abnormal maturation, acceleration of enzyme degradation, and direct modulation of catalytic activity. The TYR activity modulators were reported to treat hyper- and hypo-pigmentary skin disorders (Pillaiyar et al., 2017). These TYR enzyme inhibitors are commonly used in commercial cosmetics, mainly as a skin whitening agent (Pillaiyar et al., 2017). These medicinal plants and their phytochemicals showing inhibitory and stimulatory effect on TYR are shown in **Tables 2 and Table 3**.

Conversely, many inhibitors targeting TYR have been reported to exhibit lesser adverse effects (Burnett et al., 2010). Intriguingly, it has been revealed that some of the glycosylation inhibitors, glucosamine, and tunicamycin, do not affect TYR expression, but inhibit the synthesis of melanin (Swanson et al., 2001). Together, diverse research approaches are warranted since the conventional methods of TYR enzyme modulators have challenged its effects in melanoma therapy. Consequently, the current discoveries in melanoma therapy are

advancing by embracing technology, including nanotechnology-assisted targeted delivery (Swanson et al., 2001).

1.9.1. POMC gene expression and peptides production in C57BL/6 Mice

POMC is regulated by CRH signal that affects the function of melanocytes and melanoma cells (Slominski et al., 2013). Furthermore, the role of POMC-derived peptides in the regulation of melanogenesis is well illustrated in POMC knock out C57BL/6 mice model. The results showed that the POMC transcription of C57BL/6 mice skin is 0.9 kb long, and the POMC protein, detected with an anti-□-endorphin antibody, which has a molecular mass of 30–33 kDa (Slominski et al., 1992). This form of POMC mRNA has been observed in the epidermis and epidermal Thy-11 dendritic cells in C57BL/6 mice skin (Farooqui et al., 1993; Farooqui et al., 1995; Slominski et al., 2000). Slominski, demonstrated the effect on non-agouti C57BL/6 mice, which are POMC deficient, where the skin types are negative for mRNA, whereas the melanin pigmentation are similar to that of the control C57BL/6 $POMC^{+/+}$ and wild-type C57BL/6 mice. Therefore, C57BL/6 $POMC^{-/-}$ mice produces eumelanin hair pigmentation, in absence of local and systemic αMSH or ACTH ligands (Slominski et al., 2005). Various others studies showed that αMSH and ACTH could regulate melanin pigmentation in rodents and humans (Nordlund et al., 1988; Lerner, 1993; Slominski et al., 2000). These effects of melanocortin peptide are mediated by signal cascades that includes their binding to G protein-coupled MC1-R, activation of cAMP-dependent pathways, and stimulation or induction of eumelanogenesis (Nordlund et al., 1988; Slominski et al., 2000; Busca and Ballotti, 2000). The eumelanogenic pathway is altered by agouti protein (AGP), via both functional antagonist of melanocortins and inverse agonist, which inhibits the expression and activity of melanogenesis-related proteins, melanogenic enzymes, and MC1-R, and thereby acts as a switch between eu- to pheomelanogenesis (Hearing, 1999; Barsh, et al., 2000; Wolff, 2003; Rouzaud et al., 2003). Also, note that the switch between pheo- to

572 eumelanogenesis in normal agouti is a discontinuous process, usually produced at low levels
573 of TYR activity (Oyehaug et al., 2002).

574 A recent report proposed on the role of p53, a key regulator agent for pigmentary
575 responses in tanning and pigmentation (Cui et al., 2007). Cui et al., proposed on the UV
576 induction of POMC including α-MSH and □-endorphin, which is directly controlled by p53,
577 and proposed that tanning from UVR is started by the activation of p53-mediated POMC
578 promoter (Cui et al., 2007). As illustrated in **Figure 2,** UV-induced DNA damage stabilizes the
579 tumor suppressor protein p53. However, this hypothesis is questionable since POMC knockout
580 C57BL/6 mice (the same strain used by Cui et al.,) possessed normal capability of melanin
581 pigment production (Slominski et al., 2004; Slominski et al., 2005a). This obtained result
582 decreases the strength of Cui's concept and also questions the validity of the proposed suntan
583 response and pathological hyperpigmentation (i.e., UV - p53 - POMC - melanin pigmentation).
584 Later, Slominski and their co-workers have published evidence to support the hypothesis that
585 it may not be POMC and its products, but rather the MC1-R that could be the key regulator of
586 pigmentation reported in mice (Slominski et al., 2007). On this background, we consider it
587 more likely that p53 acts as one important coordinator, but not the main or sole regulator of
588 pigmentation in the suntan response and pathological hyperpigmentation.

589 In case of the absence of POMC, it did not result in any changes in the melanogenesis,
590 when compared with the C57BL/6 mice measured using electron paramagnetic resonance
591 (EPR) spectroscopy, as well as morphologic and histological examinations. It is noted that the
592 eumelanogenic phenotype in C57BL/6 $POMC^{-/-}$ mice expresses MC1-R. Mutations in the
593 MC1R gene leads to fair skin in humans, which is also seen with inactivating human POMC
594 gene mutations. MC1R mutant receptor expression showed changes in the receptor activity,
595 which is also listed as one of the etiologic factors responsible for an increased incidence of
596 melanoma (Han et al., 2006; Rees, 2004). Therefore, these collated findings concluded that the

overwhelming dominance of POMC-derived peptides in the stimulation of melanogenesis, skin and hair pigmentation are complex in polygenic traits (Slominski et al., 2004).

1.9.2. *In-vitro* and clinical reports on melanogenesis

Slominski et al., reported on different methods to inhibit melanogenesis and showed immunosuppressive and mutagenic effect, which could alter the cellular metabolism. Melanin helps to protect against malignant melanocytes via chemo, radio, and photodynamic therapy and proposed to inhibit melanogenesis and also reduces the probability of melanoma progression (Slominski et al., 1998). Slominski et al., have studied its effect in human melanoma cells (SKMEL-188) by producing melanin pigment using tyrosine levels. The results showed that the pigmented melanoma cells were significantly less sensitive to cyclophosphamide and also kills the action of IL-2-activated peripheral blood lymphocytes. This inhibition of melanogenesis can be achieved either by blocking TYR site or chelating Cu ions to the cytotoxic action of cyclophosphamide towards melanoma cells, and also activates the IL-2 in the lymphocytes. The exogenous L-DOPA inhibits the proliferation of lymphocyte causing cell cycle arrest in G1/0 phase and also inhibits the production of IL-1□, TNF-α, IL-6 and IL-10, respectively. Thus, the cytotoxic action of cyclophosphamide could not impair the active melanogenesis, but it also possesses immunosuppressive activity. Therefore, this resistance to a chemotherapeutic or immunotoxic activity of lymphocytes could be reversed by TYR inhibitors (Slominski et al., 2009). In another study by Slominski et al., showed to inhibit the behaviour of melanogenesis in regulation with melanoma by altering the expression of HIF-1α and its related pathways. The study was carried out using human (SKMEL-188) and hamster (AbC1) melanoma cells for their activity using cell culture methods. The results showed to significantly increase the melanin pigmentation of HIF-1α, in both the cells. In cultured cells, the result on melanogenesis were significantly stimulated by the expression of HIF-1-dependent target genes that play an important role in angiogenesis and cellular metabolism.

Therefore, they have concluded that induction of melanogenic pathway could lead to elevated HIF-1-dependent and independent pathways in cultured melanoma cells, suggesting a key role for the regulation of cellular metabolism in melanogenesis (Slominski et al., 2014).

Brożyna et al., reported the effects and survival of melanogenesis in patients with stage III and IV melanoma. The samples were collected from American Joint Committee in 20 patients from stage I, 24 patients from stage II, and 29 patients from stage III cancers and the results were analysed by Prof Franciszek Łukaszczyk Memorial Hospital, Oncology Centre, Bydgoszcz, Poland. The results showed that the patients with metastatic disease, and those with melanomas exhibit significant disease-free survival than those with amelanotic lesions. Thus, melanogenesis shortens overall survival in patients with metastatic melanoma. Therefore, the authors concluded that inhibiting the process of melanogenesis appears to be an interesting approach for the treatment of metastatic melanoma (Brożyna et al., 2013). In another study by Brożyna et al., studied the activity of melanin content in metastases melanoma and its effect in radiotherapy using cohort study with two melanoma patients that were diagnosed and treated at the Oncology Centre in Bydgoszcz, Poland. The study results showed significant decrease in the melanin pigmentation in pT3 and pT4 melanomas in comparison to pT1 and pT2 tumors, respectively. However, melanin levels were measured in pT3-pT4 melanomas developing metastases stage (pN1-3, pM1) were found to be higher in pN0 and pM0 cases. Therefore, the results concluded that the presence of melanin in metastatic melanoma cells decreases the outcome of radiotherapy, and melanin synthesis that is related to higher disease advancement (Brożyna et al., 2016). Based on our cell-based and clinical research and present research we also suggest that inhibition of melanogenesis can improve radiotherapy modalities.

1.10. Discussion and Conclusion

Progress in the treatment of melanoma begins with identifying a specific target involved in the melanoma pathogenesis, and one such interesting target is by altering the TYR enzyme

(Hodi et al., 2010). The use of pro-drugs could also be a newer and interesting approach in the treatment of melanoma, but it tends to form toxic metabolites and thus requires alternative therapy (Rooseboom et al., 2004; Gasowska-Bajger and Wojtasek, 2008; Jawaid et al., 2009). Therefore, given that TYR reported to have a pivotal activity as a natural photo-protection of the skin, where several intrinsic and extrinsic factors that could influence its function, and it is also critical to understand the precise mechanisms of onset and progression of melanoma. While the etiological aspect is still unclear, were still it is believed that the DNA damage in the melanocyte is the leading cause of melanocyte's transformation and progression to melanoma.

The UVR from sun is one of the primary ecological reasons in the development of melanoma, which proliferates due to UVR -induced DNA mutations that occur in skin. The UV plays an important role in the brain and central neuroendocrine system in order to reset body homeostasis (Slominski et al., 2018; Skobowiat et al., 2011). Also, Slominski and their co-workers stated that melanoma can affect some central neuroendocrine axes and how cancer hijacks the body's homeostasis through the neuroendocrine system (Slominski et al., 2023). The epidermal melanocytes, are pigment producing cells of neural crest origin that communicates with multiple targets. Therefore, alterations in the epidermal melanocytes can affect the cutaneous functions (Slominski et al., 1993). Therefore, this leads to the activation of POMC and release of MSH from the keratinocytes, and increases the cAMP levels, which further activates the MITF transcription (Cui et al., 2007; Garibyan and Fisher, 2010). This results in the synthesis of melanin from TYR and protects from DNA damage. In keratinocytes, exposure of UVR activates NOS type 1, which leads to increased nitric oxide and TYR levels and subsequent acceleration of melanogenesis and also elevates the cofactors such as NADPH and 6-BH4 (Roméro-Graillet et al., 1997). Later on, Cannon-Albright et al., reported that exposure to UVR in patient with "9p-linked" gene were altered, which further gives us hint that mutations may also occur due to hereditary reason. The most commonly identified mutations

in melanoma are *CDKN2A* and CDK4, where mutations in the *CDKN2A* gene results in a defective p14 and p16, which is stabilized by p53 (Mehnert and Kluger, 2012). Davis et al., reported that mutations in the NER pathway could develop the risk of melanoma and showed that NER pathways increase the UVR-induced unrepaired DNA damage (Davis et al., 2019). There are other signalling pathways such as *BRAF, NRAS, NF1, PTEN, TP53, TERT, ARID2* and *MAPK*, which also showed in altering these genes that are associated with melanoma.

TYR is a rate-limiting step in the melanin production, where it catalyses L-tyrosine to L-DOPA. Thus, it could be targeted to inhibit the irregular melanin synthesis and the pathogenesis of melanoma (Buitrago et al., 2016; Pillaiyar et al., 2017; Van Staden et al., 2021). Slominski et al., reported that both L-tyrosine and L-DOPA, serves as an intermediate for melanogenesis, and acts as bioregulatory agents that helps to regulate the cellular functions (Slominski and Paus, 1990; Slominski et al., 2012). The TYR catalyses via three distinct melanogenic pathways i.e., hydroxylation of L-tyrosine, dehydrogenation of L-DOPA, and dehydrogenation of DHI, which involves exchange of electrons with copper atoms that generates orthoquinone and water as final products (Slominski et al., 2004). The TYR is expressed in two forms of protein TYRP1 and TYRP2. Defects in the TYR gene leads to a condition called negative oculocutaneous albinism type 1 (OCA1) (Tomita et al., 1989; Takeda et al., 1990; Oetting and King, 1999). Thus, in oculocutaneous albinism type 3 (OCA3), the TYRP1 is mutated within the ER and the normal processing of TYR is terminated leading to proteasomal degradation and thus reduces pigmentation (Kushimoto et al., 2003; Toyofuku et al., 2001a; Toyofuku et al., 2001b). In case of oculocutaneous albinism type 2 (OCA2) and type 4 (OCA4), the TYR from trans-Golgi Network (TGN) to melanosomes is disrupted (Chen et al., 2002; Toyofuku et al., 2002; Costin et al., 2003; Kushimoto et al., 2003). Therefore, the experimental evidence in melanocytes targeting melanosomes, shows that ER is an essential step for TYR maturation, which is important in the production of melanin pigments (Halaban,

2000; Halaban, 2002; Halaban et al., 2002a; Halaban et al., 2002b; Halaban et al., 1997; Halaban et al., 2000). Thus, defects in OCA1 via OCA4 shows melanogenic activity *in-vivo*, via posttranslational pathways, which is an important step in the processing of TYR. The MITF transcription factor regulates the MRGE expression in cultured melanoma, and showed to increase the glycosylation of TYR in the ER, which results in pigmentation (Imokawa, 1989). In TYR, the ERAD is regulated by ubiquitin-proteasome system, E3 ligases Doa10p and Hrd1p, which results in degradation (Hammond and Helenius, 1995; Bordallo et al., 1998). Thus, mutations in TYR result in TYR sequestration in the ER and is degraded through ERAD by inhibiting its functions (Smith et al., 2004). Therefore, ER plays a significant role in the regulation of TYR. Our review collated that various approaches to regulate the abrupt melanogenesis in melanoma and could modulate the TYR enzyme levels or activity. However, the clinical safety of TYR modulators in both acute and long-term use is an evolving area of research focus in the fields of skin cancer therapeutics.

As we discussed, the POMC is regulated by CRH, which affects the functions of melanocytes and melanoma cells (Slominski et al., 2013). The regulation process by external agents such as α-MSH and its antagonist agouti, are both mediated by the MC1-R at the surface of the melanocyte. A mathematical model is developed to improve our understanding of melanogenic switching, i.e., agouti background, which acts as a switch between eumelanin and pheomelanin production depending on the extracellular signaling context (Oyehaug et al., 2002).

As reviewed, selective findings have provided intriguing leads and that warrant further research and a clear understanding of the critical roles of TYR in cell signaling pathways controlling melanogenesis. Delineation of these leads may unravel new therapeutic targets to treat melanin-related pigmentary disorders and melanoma. Nonetheless, our review collates that the TYR enzyme exhibits a critical role in paving melanoma's pathogenesis and is a

potential druggable target to combat melanoma. However, the quest to unravel the clinically safe TYR modulators remains elusive.

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Author Contribution

Rajan Logesh - Conceptualization; **Rajan Logesh, Sagar Rajendra Prasad** - Data curation; Writing - review & editing; **Nirmal Robinson** - Methodology; **Sandhya Chipurupalli** - Software; **Nirmal Robinson** and **Suresh Kumar Mohankumar** – Supervision.

Conflict of Interest

The authors declare no competing financial interest.

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Figure Captions

Fig. 1. Risk factors of melanoma. UV radiation is the major environmental factor affecting melanoma. Other risk factors include skin phenotype, number of naevi and chemical pollutants like arsenic; Germ-line mutations in genes regulating cell cycle arrest & DNA repair mechanism; Somatic mutations in pathways regulating cell proliferation, growth & metabolism, and oncogenic signalling.

Fig. 2. Role of Tyrosinase in melanin synthesis: Conversion of L-tyrosine to L-DOPA is the rate-limiting step in melanin synthesis, and this step is catalyzed by the enzyme Tyrosinase. It further converts L-DOPAse to DOPA-quinone, which in turn follows a sequence of steps catalyzed by Tyrosinase and forms DHI Melanin (Black), DHICA Melanin (Brown). In the presence of cysteine or glutathione, DOPA-quinone is sequentially converted to Pheomelanin

(Yellow to Red) which is independent of Tyrosinase. The region highlighted in orange colour shows the steps catalysed by Tyrosinase.

Table Captions

Table 1. List of components inhibiting the TYR expression level.

Table 2. List of reported phytochemicals showing Tyrosinase inhibitory activity with their IC_{50} values.

Table 3. List of reported medicinal plant's showing Tyrosinase inhibitory activity with their IC_{50} values.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The authors have no competing financial interests or personal interest.